Cuk-H022-74-48 P.3.12 9/76

The American Journal of Cardiology

48

JANUARY 2, 1990

A Symposium: Controlling Cardiac Arrhythmias with Sotalol, a Broad-Spectrum Antiarrhythmic with Beta-Blocking Effects and Class III Activity

GUEST EDITOR:
Bramah N. Singh, MD, DPhil
Veterans Administration Medical Center of West Los Angeles and
UCLA School of Medicine, Los Angeles, California

A YORKE MEDICAL JOURNAL/CAHNERS PUBLISHING COMPANY

The American Journal of Cardiology

JANUARY 2, 1990 VOL. 65 NO. 2

A Symposium: Controlling Cardiac Arrhythmias with Sotalol, a Broad-Spectrum Antiarrhythmic with Beta-Blocking Effects and Class III Activity

GUEST EDITOR:

Bramah N. Singh, MD, DPhil
Veterans Administration Medical Center of
West Los Angeles and UCLA School of Medicine
Los Angeles, California

This symposium was held on November 13, 1988, in Washington, D.C.,
and was supported by an educational grant from Bristol-Myers Company.

EDITOR-IN-CHIEF
William C. Roberts, MD

MANAGING EDITOR, SPECIAL PROJECTS
Judith Wagner

PUBLISHER, SPECIAL PROJECTS
Kenton T. Finch

PRODUCTION EDITOR
Vicky Weisman

PROOF EDITOR
Mary Crowell

THE AMERICAN JOURNAL OF CARDIOLOGY.® (ISSN 0002-9149) January 2, 1990, Vol. 65, No. 2 (USPS: 505–750).

Member, American Business Press, Inc. and Audit Bureau of Circulations. Published 4 times in January, February, June, July, September and October, 3 times in March, April, May, August and November, and 2 times in December, by The Cahners Publishing Company, a Division of Reed Publishing USA, 275 Washington St., Newton, MA 02158-1630. Terrence M. McDermott, President; Jerry D. Neth, Vice President/Publishing Operations; J.J. Walsh, Financial Vice President/Magazine Division; Thomas J. Dellamaria, Vice President/Production and Manufacturing.

SUBSCRIPTIONS: Solicited only from cardiologists and other physicians. Publisher reserves the right to refuse unqualified subscribers. Subscribers agree that no article or any part thereof published in any editions of the American Journal of Cardiology received under this subscription agreement may be copied, recorded or reproduced in any form or by any means, electronic or mechanical, including, among other things, photocopying or the storing of part or all of such articles on any information retrieval system, without the written permission of the Publisher. Address correspondence regarding subscriptions and changes of address to: THE AMERICAN JOURNAL OF CARDIOLOGY, 44 Cook Street, Denver, Colorado 80206-5800 (1-800-327-9021). Please include your zip code and, in case of change of address, copy of old address label. Changes of address must reach the Journal one month preceding month of issue. Single copy price: Regular issues $10.00; Symposium and special issues $12.00. Subscription rate for individuals in field of publication: United States 1 year $66, 2 years $112, 3 years $158; Canada and all other countries 1 year $105, 2 years $178, 3 years $252; Residents and Medical Students: United States 1 year $33; Canada & all other countries 1 year $85. Institutions: United States 1 year $95, 2 years $162, 3 years $228; Canada & all other countries 1 year $125, 2 years $213, 3 years $300. Air Mail available at additional charge of $150 per year. The Journal is not responsible for replacing missing issues unless the Circulation Department is notified of nonreceipt within 3 months of issue date.

Second class postage paid at Denver, CO, and at additional mailing office. Printed in U.S.A. Trademark™ in U.S. Patent Office. © Copyright 1990 by Reed Publishing USA: Saul Goldweitz, Chairman; Ronald G. Segel, President and Chief Executive Officer. All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording or by any information storage retrieval system, without permission of the copyright owner. Prices on bulk reprints of articles available on request.

The Publisher assumes no liability for any material published in the Journal. All statements are the responsibility of the authors.

MANUSCRIPTS: Address all manuscripts to William C. Roberts, MD, Editor-in-Chief, the American Journal of Cardiology, 7960 Old Georgetown Road, Suite 2C, Bethesda, Maryland 20814.

POSTMASTER: Send address changes to: The American Journal of Cardiology, 44 Cook Street, Denver, Colorado 80206-5800.

Cahners Publishing Company, A Division of Reed Publishing USA □ Specialized Business Magazines for Building & Construction □ Manufacturing □ Foodservice & Lodging □ Electronics & Computers □ Interior Design □ Printing □ Publishing □ Industrial Research & Technology □ Health Care □ Entertainment.

Publisher's Note

The opinions expressed in this presentation are those of the panelists and are not attributable to the sponsor or the publisher, editor, or editorial board of The American Journal of Cardiology. Clinical judgment must guide each physician in weighing the benefits of treatment against the risk of toxicity. References made in the articles may indicate uses of drugs at dosages, for periods of time, and in combinations not included in the current prescribing information.

Editor's suggestion: The symposium issues for a full year should be bound together separately from the regular issues.

CALCUTTA UNIVERSITY CENTRAL LIBRARY

P 24, 176

CONTENTS

The American Journal of Cardiology

JANUARY 2, 1990 VOL. 65 NO. 2

A SYMPOSIUM: CONTROLLING CARDIAC ARRHYTHMIAS WITH SOTALOL, A BROAD-SPECTRUM ANTIARRHYTHMIC WITH BETA-BLOCKING EFFECTS AND CLASS III ACTIVITY

1A
Introduction
Bramah N. Singh

3A
Historical Development of the Concept of Controlling Cardiac Arrhythmias by Lengthening Repolarization: Particular Reference to Sotalol
Bramah N. Singh

12A
Pharmacology, Pharmacodynamics and Pharmacokinetics of Sotalol
Michael J. Antonaccio and Allen Gomoll

22A
Concentration/Response Relations for the Multiple Antiarrhythmic Actions of Sotalol
Raymond L. Woosley, Jean T. Barbey, Ted Wang, and Christian Funck-Brentano

28A
Hemodynamic Effects of Intravenous and Oral Sotalol
John J. Mahmarian, Mario S. Verani, and Craig M. Pratt

35A
Discussion I: Pharmacology, Pharmacodynamics and Pharmacokinetics of Sotalol

37A
Effectiveness of Sotalol for Therapy of Complex Ventricular Arrhythmias and Comparisons with Placebo and Class I Antiarrhythmic Drugs
Jeffrey L. Anderson

43A
Suppressant Effects of Conventional Beta Blockers and Sotalol on Complex and Repetitive Ventricular Premature Complexes
Prakash C. Deedwania

51A
Discussion II: Sotalol and Suppression of Ventricular Premature Complexes

53A
Effects of Sotalol on Ventricular Tachycardia and Fibrillation Produced by Programmed Electrical Stimulation: Comparison with Other Antiarrhythmic Agents
Koonlawee Nademanee and Bramah N. Singh

58A
Safety and Efficacy of Sotalol in Patients with Drug-Refractory Sustained Ventricular Tachyarrhythmias
Richard F. Kehoe, Terry A. Zheutlin, Cathy S. Dunnington, Thomas A. Mattioni, George Yu, and Robert B. Spangenberg

65A
Discussion III: Effects in Malignant Ventricular Arrhythmias

67A
Sotalol for Paroxysmal Supraventricular Tachycardias
A. John Camm and Vince Paul

74A
Clinical Safety Profile of Sotalol in Patients with Arrhythmias
Lester F. Soyka, Carol Wirtz, and Robert B. Spangenberg

82A
Discussion IV: Supraventricular Arrhythmias

84A
Expanding Clinical Role of Unique Class III Antiarrhythmic Effects of Sotalol
Bramah N. Singh

The American Journal of Cardiology

Introduction

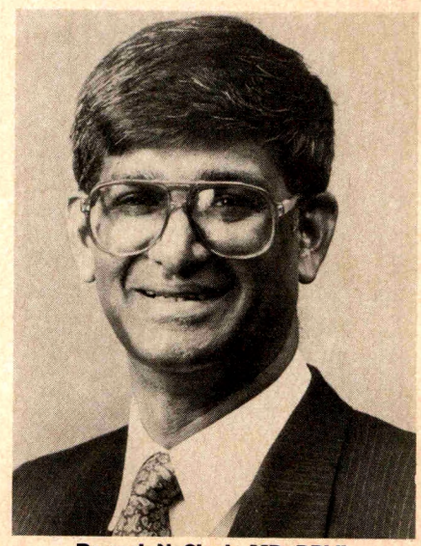
Bramah N. Singh, MD, DPhil

Drug therapy of cardiac arrhythmias is clearly at a crossroads. It is almost 20 years since Vaughan Williams and I suggested that selectively prolonging cardiac repolarization represented a discrete antiarrhythmic mechanism—the so-called class III action. This idea stemmed from electrophysiologic studies involving the effects of sotalol in isolated cardiac muscle. Although the concept was intrinsically attractive, it did not have immediate clinical appeal. Indeed, it drew little attention until amiodarone, another compound that, in our studies, also appeared to act by prolonging repolarization, was found by Mauricio Rosenbaum in Argentina to be unusually effective in controlling recalcitrant ventricular and supraventricular tachyarrhythmias. A resurgence of interest in sotalol as a class III antiarrhythmic compound is therefore logical and timely. It combines β-blocking and class III actions with a side-effect profile that is more benign and predictable than that of amiodarone.

A review of the pharmacodynamics and pharmacokinetics of sotalol and its emerging role in the control of a broad spectrum of cardiac arrhythmias was held during a half-day symposium on November 13, 1988, in Washington, D.C., immediately preceding the Annual Scientific Meeting of the American Heart Association. The program, made possible by an educational grant from Bristol-Myers Company with the organizational assistance of Raven Health Care Communications, New York, brought together investigators of international reputation as participants. The peer-reviewed and edited version of the symposium proceedings, including discussions, is the basis of this supplement.

A clear understanding of the theoretical basis and the experimental and the clinical validation of the concept of controlling cardiac arrhythmias by lengthening repolarization is essential background to the subject. This is provided at the outset with a brief historical perspective and an emphasis on the salient features of the electrophysiologic properties of sotalol. Antonaccio and Gomoll review both old and new data on the pharmacodynamics and pharmacokinetics of the drug; they indicate that the lower-than-expected propensity of sotalol to depress ventricular myocardium is a function of the drug's action to prolong cardiac repolarization. Woosley et al present data dealing with concentration-response relations of sotalol. They raise the possibility that d-sotalol might lower heart rate directly as a consequence of its class III action, a controversial issue that needs to be resolved, possibly by the use of the so-called "pure" class III agents. Heart rate reduction by an antiarrhythmic agent is an important issue. Mahmarian et al confirm that, as in the case of experimental animals and isolated tissues, sotalol has much less of a myocardial depressant effect than do conventional β blockers. These findings are in accord with the known electrophysiologic and inotropic characteristics of class III agents in general.

An important issue that has come into sharp focus since the symposium is whether the suppression of ventricular premature complexes (VPCs) might prolong survival in subsets of patients at high risk for sudden death. The Cardiac Arrhythmia Suppression Trial (CAST) has since showed that, at least in the case of drugs that markedly delay conduction, the sudden death rate may be enhanced. From numerous β-blocking trials not designed to test the effect of arrhythmia suppression on mortality, it is well known that these agents do reduce sudden death in survivors of acute infarction. Therefore VPC suppres-



Bramah N. Singh, MD, DPhil

From the Veterans Administration Medical Center of West Los Angeles and the UCLA School of Medicine, Los Angeles, California.

Address for reprints: Bramah N. Singh, MD, Section of Cardiology 691/111E, Wadsworth Veterans Administration Hospital, Wilshire and Sawtelle Boulevards, Los Angeles, California 90073.

sion remains of interest in this context. Anderson presents data on the comparative efficacy of sotalol and certain class I agents, and Deedwania describes the relative effects of conventional β blockers and sotalol on VPCs. Whether the differences that clinical trials of this kind might reveal are clinically significant remains to be determined.

Perhaps the most striking and clinically meaningful difference clearly emerging between conventional β blockers and sotalol is the efficacy of sotalol in symptomatic sustained ventricular tachycardia or fibrillation and in survivors of sudden cardiac death. Nademanee and I and Kehoe et al present data indicating that sotalol is at least as effective as class I agents in these patients. Camm and Paul succinctly review the available data on the expanding role of sotalol as a class III agent in the treatment of supraventricular arrhythmias. The data provide a basis for critically testing the relative merits of delaying conduction vs prolonging refractoriness as determinants of success in controlling such arrhythmias. Finally, Soyka et al review the extensive data now available on the adverse effects of sotalol. It is particularly interesting that, despite the striking lengthening of the QT interval and the accompanying bradycardia that sotalol induces, the incidence of torsades de pointes—the specific proarrhythmia characteristic of class III agents—does not exceed 5%.

As indicated in the final presentation, this series of reports delineates the expanding role of the unique class III antiarrhythmic effects of sotalol. More than that, it points to a new focus for the pharmacologic control of cardiac arrhythmias: altering the myocardial substrate by prolonging repolarization rather than by greatly delaying conduction to eliminate the trigger mechanisms.

Historical Development of the Concept of Controlling Cardiac Arrhythmias by Lengthening Repolarization: Particular Reference to Sotalol

Bramah N. Singh, MD, DPhil

Although numerous pathophysiologic states, such as hypocalcemia and hypothyroidism, lengthen repolarization and are associated with a reduced incidence of cardiac fibrillation, the concept of the pharmacologic control of rhythm disorders by prolonging the action potential duration is relatively new. There is now a great deal of interest in the relative merits and applicability of delaying conduction or prolonging refractoriness as ways to prevent arrhythmias. Prolonging the action potential duration in cardiac tissues lengthens the refractory period without affecting conduction, prolongs the cycle length of the tachycardia, and prevents it from deteriorating into fibrillation. Lengthening the action potential duration is also associated with a positive inotropic effect demonstrated most readily in isolated cardiac tissues, an important feature in antiarrhythmic agents intended for use in life-threatening tachyarrhythmias in patients with reduced ventricular function. This array of properties was first recognized in the β blocker sotalol and formed the basis for a discrete class of antiarrhythmic mechanism—the so-called class III electrophysiologic effect. Such a series of actions was also recognized early in the case of amiodarone, which has a much more complex pharmacologic profile. Clinical studies with sotalol and amiodarone have done much to establish the clinical use of prolonging the action potential duration in controlling a broad spectrum of cardiac arrhythmias. Both amiodarone and sotalol prolong the action potential duration and attenuate adrenergic stimulation, but they do so by fundamentally different mechanisms.

The electrophysiologic properties of sotalol represent the combined effects of β blockade and lengthening the action potential duration. Prolonging the action potential duration is not related to β blockade because the dextroisomer of the compound has effects identical to those of the levoisomer at the same drug concentrations. In high concentrations, sotalol inhibits the inward sodium current but does not affect the inward slow calcium current. It prolongs repolarization by inhibiting the delayed rectifier potassium current, with a modest effect on the inward rectifier. After intravenous or oral administration in humans, sotalol slows the heart rate and intranodal conduction and prolongs the refractory period in the atrioventricular node. These effects are due essentially to β blockade and are similar to those produced by most heart rate–reducing β blockers. The class III actions of sotalol are reflected in the prolongation of the monophasic action potential duration accompanied by major increases in the refractory periods in the atria, ventricles, His-Purkinje system, and in the bypass tracts in both the retrograde and anterograde directions. These changes occur independently of β blockade. The available data on the pharmacodynamic and electrophysiologic properties of sotalol suggest that the drug's action should result in the acute and prophylactic control of a wide variety of supraventricular and ventricular arrhythmias.

(Am J Cardiol 1990;65:3A–11A)

The electrophysiologic concept that cardiac arrhythmias may be aborted by lengthening the repolarization phase of the cardiac action potential is not new. Not long after quinidine was introduced into therapeutics, Lewis et al[1,2] described its clinical use in atrial fibrillation and suggested that it acted by increasing the refractoriness of cardiac muscle. While being consistent with the idea that atrial fibrillation was based on a "circus" movement in the atria, the suggestion was also appealing since the most readily measurable effect of quinidine was the prolongation of the QT interval on the surface electrocardiogram.

No further advances in understanding how quinidine exerted its beneficial effects in controlling arrhythmias were made for 3 decades. The electrical activity of the heart could then be studied by applying the microelectrode technique to isolated cardiac muscle. In the 1950s, a number of investigators,[3–6] particularly Vaughan Williams,[5] showed that quinidine, in clinically meaningful concentrations, had the dominant effect of depressing the

From the Division of Cardiology, Veterans Administration Medical Center of West Los Angeles, and the Department of Medicine, the University of California at Los Angeles School of Medicine, Los Angeles, California. This study was supported in part by grants from the Medical Research Services of the Veterans Administration and the American Heart Association of the Greater Los Angeles Affiliate.

Address for reprints: Bramah N. Singh, MD, Section of Cardiology 691/111E, Wadsworth Veterans Administration Hospital, Wilshire and Sawtelle Boulevards, Los Angeles, California 90073.

maximal rate of rise of the cardiac action potential rather than lengthening repolarization. Conduction velocity was markedly slowed, while only the terminal portion of repolarization was modestly lengthened. There was little effect on the plateau phase of the action potential. Thus, it appeared that quinidine had little effect on the absolute refractory period; it could, however, influence the effective refractory period by 2 distinct mechanisms. First, as shown by Weidmann,[3] the drug shifted the curve relating the maximal rate of rise of the action potential to the membrane voltage in the hyperpolarizing direction. This effect was similar to that produced by low-sodium media. Thus, a critical time-dependent recovery of the sodium carrier mechanism was necessary before the next propagated action could be elicited in response to an applied extrastimulus.[7] Second, Weidmann[3] found that the cardiac membrane needed to repolarize to a certain minimal voltage before a response to a stimulus could be obtained. Therefore, interventions that prolonged the action potential duration were likely to lengthen cardiac refractoriness. These 2 ways in which cardiac refractoriness can be altered have since been designated as time- and voltage-dependent mechanisms. A careful analysis of the action of quinidine in terms of its concentration-effect relations has shown that its major influence is on depolarization rather than repolarization. In the decade that followed the aforementioned classic observations in the microelectrode laboratory, the major focus was essentially on the time-dependent mechanism for an increase in refractoriness as an antiarrhythmic action.[8]

The question of whether lengthening the effective refractory period by prolonging the cardiac action potential itself (without an associated change in the rate of rise of the action potential) might be a discrete antiarrhythmic mechanism became clouded by the reports of sudden deaths that complicated the long QTc-interval syndromes.[9,10] Schwartz[11] reviewed the subject, and Surawicz and Knoebel[12] recently discussed the circumstances in which lengthened QTc interval is associated with an enhanced tendency for the occurrence of atypical ventricular tachycardia. However, there appears to have been less emphasis on the clinical instances in which lengthening the cardiac action potential has been associated with a reduced probability of cardiac arrhythmias.

Such clinical entities are nevertheless important because they may provide models elucidating the potential mechanisms whereby prolonging cardiac repolarization might constitute an antiarrhythmic effect. Interest recently burgeoned in this area, undoubtedly because amiodarone, the dominant electrophysiologic action of which is to lengthen the cardiac action potential during chronic administration, has been found to be an unusually potent agent for controlling most cardiac arrhythmias.[13] Various lines of evidence recently converged to indicate that the lengthening of the action potential duration provides an important mechanism for controlling cardiac arrhythmias.[14] Because this subject was discussed at length in a recent monograph[15] and in an editorial,[16] only the salient features will be considered.

LENGTHENING OF ACTION POTENTIAL DURATION AS AN ANTIARRHYTHMIC MECHANISM

As early as 1955, Weidmann[3,7] clearly established the voltage dependence of the heart's refractory period. He showed that in Purkinje fibers under voltage-clamp conditions, the membrane potential needed to return to at least −55 mV (after a driven action potential) before another action potential could be elicited. The electrophysiologic implications of this observation are obvious. Thus, physiologic, pharmacologic or pathologic interventions tending to shorten the time course of repolarization would, of necessity, abbreviate the refractory period of cardiac muscle and would likely be arrhythmogenic. This has been clearly established for anoxia, halothane and acetylcholine (in atrial muscle), all of which accelerate repolarization; they all shorten the refractory period and are known to be arrhythmogenic or cause fibrillatory perturbations. For example, atrial fibrillation can be produced predictably by an atrial extrastimulus during continuous vagal stimulation.[17]

However, if one delayed attainment of a minimal level of the membrane voltage needed to generate a second action potential in response to an extrastimulus by interfering with processes that normally govern the repolarization rate, the refractory (both the absolute as well as the effective) periods of cardiac muscle would be correspondingly prolonged, an antiarrhythmic mechanism.

It should be emphasized that such a change may occur entirely independently of any alteration in cardiac depolarization and conduction velocity. However, it would produce a number of discrete electrophysiologic and inotropic effects. First, in pacemaker tissues and other fibers with potential for spontaneous automaticity, lengthening the action potential duration will delay attaining the maximal diastolic potential. The onset of the next spontaneous diastolic depolarization will be similarly retarded. Thus, the threshold voltage will be reached later and the cycle length of the tachycardia (if automatic) will be prolonged. Second, in nonpacemaker tissues, the increases in the action potential duration and in the voltage-dependent refractoriness will slow the tachycardia (regardless of its mechanism) or may make it less readily sustained. Moreover, in the case of ventricular tachycardia, prolonging the cycle length may prevent the acceleration of the tachycardia with a reduction in its tendency to deteriorate into ventricular fibrillation. Such an effect on repolarization, in the case of an intervention that has no significant depressant effect on conduction velocity, is unlikely to lead to reentrant excitation. However, this is likely to hold true only if the lengthening of the action potential duration is uniform, so that the tendency toward focal reexcitation from heterogeneity in repolarization and refractoriness resulting from nonuniform alterations in the action potential durations is avoided.

Finally, the issue of whether lengthening the cardiac action potential duration might affect cardiac contractile force is important. Experimental and clinical data suggest that antiarrhythmic agents that lengthen cardiac

repolarization are not negatively inotropic.[18] There is evidence that many of them may exert a positive inotropic action.[19] These properties are particularly useful clinically because the patients with life-threatening ventricular arrhythmias have the greatest need for aggressive pharmacologic therapy and the most compromised ventricular function.[20]

Numerous observations indicate that lengthened cardiac repolarization may be associated with enhanced contractility. For example, Kavaler[21] showed that sustained depolarization led to increased tension development in isolated heart muscle. This was confirmed by Morad and Trautwein,[22] who studied the relation between the action potential duration and contraction in mammalian cardiac muscle. Therefore, it was interesting when Singh and Vaughan Williams[23] showed that, despite the fact that sotalol is a β blocker, it did not exert a depressant effect on contractility and, in fact, in some preparations it exhibited a frankly positive inotropic effect in feline papillary muscle (Fig. 1). This was consistent with the observation of Kaumann and Olson,[24] who found that sotalol not only augmented isometric contractions in papillary muscle but also produced long-lasting aftercontractions as a function of increases in the duration of the intracellularly recorded action potentials (Fig. 2). In vivo, the positive inotropic effects of sotalol are more difficult to demonstrate because such effects may be offset by the concomitant β blockade induced by the drug. However, Brooks et al[25] reported that intravenously administered sotalol did not significantly depress systemic hemodynamics in patients with cardiac failure, in contrast to the well-known depressant effects of conventional β-blocking agents. Orally administered sotalol has been found to be reasonably well tolerated by patients with low left ventricular ejection fractions[26,27]; rarely does the drug aggravate heart failure in such patients. It appears that when it does, the withdrawal of the sympathetic drive by the drug outweighs its potential intrinsic positive inotropic actions. As indicated elsewhere, all or nearly all so-called class III antiarrhythmic drugs have a benign hemodynamic profile, even in patients with congestive cardiac failure.[18]

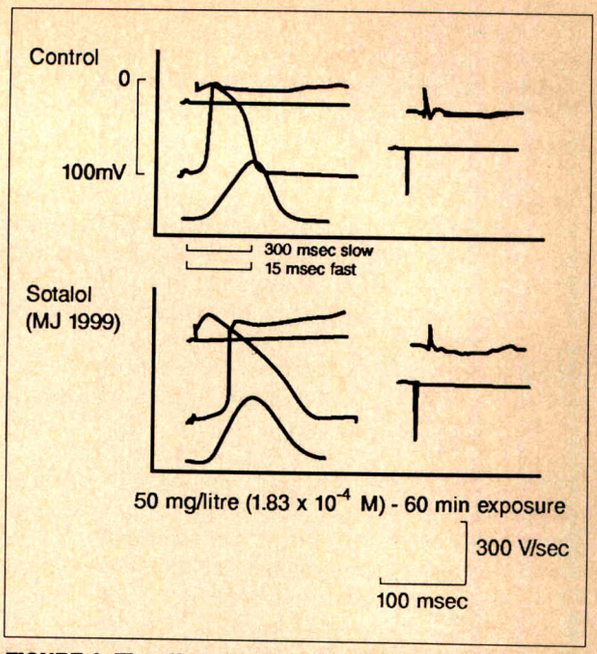


FIGURE 1. The effect of sotalol (MJ 1999) on the transmembrane action potentials recorded from feline ventricular muscle. *Horizontal line* on the left at the top of each panel represents zero potential; *middle trace* represents the action potential at slow and fast sweep speeds. *Bottom trace* represents isometric tension. *Upper trace* on the right represents surface potential and the *lower trace* represents the differential signal for the maximal rate of rise of the action potential. Note that sotalol has little or no effect on the upstroke velocity (maximal rate of rise) of phase 0 or on isometric tension. The dominant effect is lengthening the action potential duration and thus, by inference, the effective refractory period (a class III action). (Reprinted with permission from *Br J Pharmacol.*[23])

CLINICAL ANTIARRHYTHMIC CORRELATES OF PROLONGED CARDIAC REPOLARIZATION

For many years, certain clinical situations have been known to be associated with a reduced incidence of cardiac arrhythmias. For example, hypocalcemia homogeneously lengthens the QT interval of the electrocardiogram and arrhythmogenicity in hypocalcemic syndromes

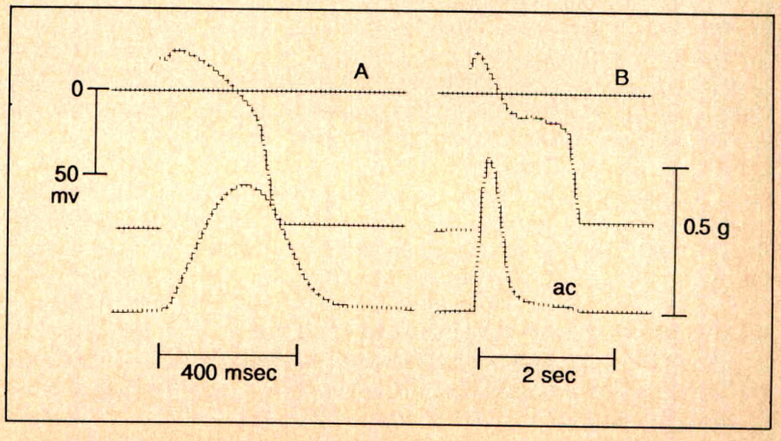


FIGURE 2. Effects of sotalol (27 μg/ml) on the action potential isometric tension in papillary muscle from the kitten heart. *Upper trace* of each panel (*A* and *B*) show zero potential; *middle trace* the transmembrane potential; *lower trace* the isometric tension. Vertical calibration: membrane potential (*left*) and isometric tension (*right*). Horizontal calibration: time. *A*, under control conditions recording; *B*, the effects of sotalol superfusion. Note that the drug augments peak isometric tension equal to the lengthening of the action potential. An aftercontraction (ac) develops during the prolonged phase 2 of the action potential. (Reprinted with permission from *Science.*[24])

is rare unless complicated by hypokalemia. Furthermore, reducing serum calcium in certain situations (e.g., glycoside intoxication) may correct dysrhythmias. Perhaps hyperthyroidism is the most striking example of a clinical entity in which changes in the action potential duration appear correlated with the tendency for arrhythmias to develop; in such cases a marked shortening of the action potential duration of the atria has been reported[28] and may be related to the frequent paroxysmal or sustained atrial fibrillation that responds to antithyroid treatment. Conversely, in hypothyroidism, arrhythmias of any kind are uncommon. The major electrophysiologic effect of deficient thyroid hormone on cardiac muscle is "isolated" prolongation of the action potential duration with depression of phase 4 depolarization in the sinus node.[28,29] However, the latter effect may not be caused entirely by lengthening the action potential duration in the sinus node, as there is a downregulation of β receptors in hypothyroidism. The slowing of the sinus frequency may be due in part to adrenergic antagonism secondary to hypothyroidism, with a depressant effect on phase 4 depolarization. Conversely, Arnsdorf and Childers,[30] using atria from hyperthyroid rabbits, showed that the effective refractory period was much shorter than in those that were euthyroid. It is known that phase 4 depolarization is markedly steepened in hyperthyroidism.

These observations on altered thyroid state and the incidence of cardiac arrhythmias may also be related to recent observations linking the stability of sinus rhythm in patients with paroxysmal atrial fibrillation to the duration of the atrial action potential determined by intracavitary suction electrodes.[19] For example, in patients who underwent electrical conversion to sinus rhythm, the relapse rate to atrial fibrillation was significantly higher in those with shorter action potential durations.[31] Thus, these observations clearly suggest that drug-induced lengthening of the myocardial action potential duration, by whatever mechanism, should reduce the probability of cardiac fibrillation. The issue about hypothyroidism, as an example of a clinical situation with a reduced probability of cardiac fibrillation from an apparently potent class III antiarrhythmic action, has recently come into sharp focus because of growing evidence that the fundamental mechanism of action of amiodarone on repolarization might be mediated through a competitive T_3 antagonism in the myocardium.[32]

Although this issue is important in the development of class III agents that act in a similar manner to amiodarone, the effects of sotalol clearly differ from those of amiodarone. Nevertheless, they share 2 features, namely, an antiadrenergic effect associated with a reduction in heart rate and the marked prolongation of the action potential duration and refractoriness in various cardiac fibers.

DEVELOPMENT OF THE PHARMACOLOGIC CONCEPT OF CLASS III ANTIARRHYTHMIC ACTION: FOCUS ON SOTALOL

While investigating the properties of a number of β antagonists, Singh and Vaughan Williams[23] and Singh[33] found that the β-blocking drug sotalol (MJ 1999), besides having the propensity to block β receptors competitively, lengthened the intracellularly measured action potentials in mammalian myocardial fibers (Fig. 1) and prolonged the QTc interval of the surface electrocardiogram in anesthetized guinea pigs. By inference, the drug prolonged the effective refractory period. Sotalol also protected experimental animals from ventricular fibrillation due to cardiac glycoside intoxication. The overall effects of the drug could not be explained on the basis of β blockade alone or by inhibition of the fast-sodium channel. Unlike quinidine or procainamide, sotalol produced no significant changes in depolarization. Thus, it was believed at that time that sotalol exhibited electrophysiologic properties that were unique. It was postulated that the simple lengthening of the action potential duration constituted a significant and discrete mechanism (the so-called class III) for the control of cardiac arrhythmias.[23,33] Recent experimental[34] and clinical[26,27] observations tend to vindicate these earlier, somewhat theoretical expectations.

There are now a growing number of pharmacologic agents that might exert their major antiarrhythmic actions by selectively lengthening cardiac repolarization. Until recently, the most significant compounds in this class included sotalol and its isomers, amiodarone[35] and its metabolite (desethylamiodarone), N-acetylprocainamide, bretylium, pranolium, clofilium and melperone. Numerous newer compounds, such as sematilide, E-4031, and UK 68,798, among others, now are at varying stages of pharmacologic characterization and clinical evaluation. Structurally and pharmacologically, these agents are diverse. One may therefore expect significant differences with respect to their antiarrhythmic potency, pharmacokinetic properties, side-effect profiles, proarrhythmic tendencies (especially torsades de pointes) and overall clinical efficacy. However, they do share many common features with respect to their hemodynamic and electrophysiologic effects, an understanding of which may provide further insights into the nature of antiarrhythmic actions.

Only the properties of sotalol will be discussed as a preamble to this international symposium. The main purpose here is to bring together, within a convenient and a relatively brief format, the evolving role of this unique β blocker, the electrophysiologic properties of which formed the basis for the concept of controlling cardiac arrhythmias by prolonging cardiac repolarization, as was suggested 20 years ago.[23]

SOTALOL AS A BROAD-SPECTRUM ANTIARRHYTHMIC COMPOUND: ELECTROPHYSIOLOGIC BASIS

In delineating the overall properties of sotalol, it is essential to define those aspects of its antiarrhythmic actions that are caused by its β-blocking properties and those that stem from its property of lengthening cardiac repolarization. Both features constitute integral components of the drug's overall antiarrhythmic actions.

Beta-blocking potency of sotalol: Unlike other para-substituted β blockers, such as atenolol and metoprolol, sotalol is not cardioselective, nor does it exhibit intrin-

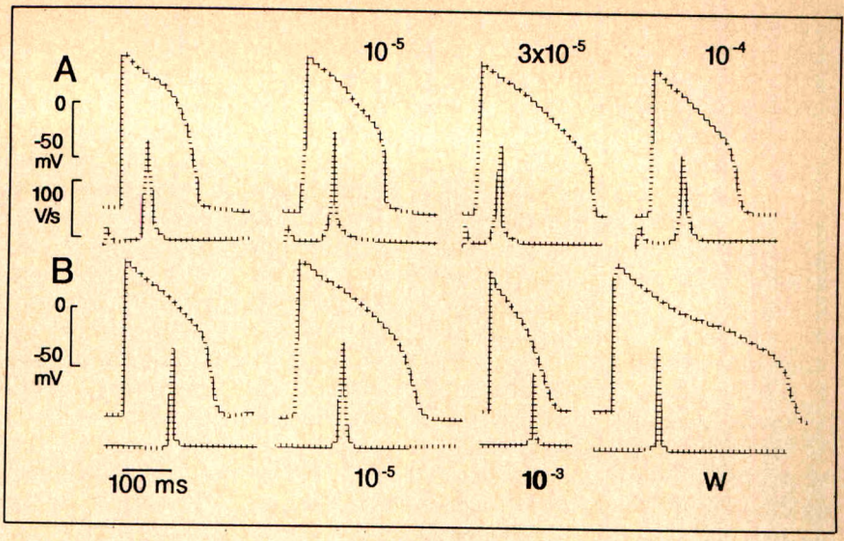


FIGURE 3. Transmembrane action potentials and the first derivative of the upstroke obtained from two (*A* and *B*) rabbit papillary muscles superfused with drug-free Tyrode's solution (*left*) and drug-containing solutions (molar concentrations given by the figures). W = action potentials during washout (the stimulation was 1 Hz). (Reproduced with permission from *J Pharmacol Exp Ther.*[49])

sic sympathomimetic activity or local anesthetic actions.[23,33,36] However, numerous in vitro and in vivo studies have clearly established its β-blocking propensity.[36–44] The commercially available preparation is the racemic mixture of d- and l-sotalol, the dextroisomer having less than one-fiftieth the activity of the levocompound.[44]

In isolated tissues, sotalol shifts the agonist dose-response curve to the right[33,38,42–48] in a parallel fashion. In the formal analysis of the differences between propranolol and sotalol as β antagonists, values of β-blocking potency for propranolol of about 8.7 and of 6.4 for sotalol have been reported, reflecting a marked difference in the relative potencies of the 2 β blockers.[38,43] However, such a 100-fold difference in the blocking actions of the 2 compounds has not always been demonstrated. Some studies[36] have shown that in vitro sotalol was one-tenth to one-fiftieth as potent as propranolol. The marked difference between the in vitro and in vivo blocking potencies of sotalol is not completely understood but has been attributed to a low lipid solubility, which is balanced by good absorption and high metabolic stability of the drug.

In intact anesthetized animals and in conscious humans, the potency ratio between sotalol and propranolol appears to be 1:3 or 1:2 to 3.[36–43] However, sotalol exerts a nonadrenergically mediated positive inotropic effect,[23,24,36,38,39] although a weak one, which may influence the precise determination of its β-blocking propensity against standard agonists such as isoprenaline.

Cellular electrophysiologic effects of sotalol: It is of historical interest that sotalol was introduced as a β blocker in the early 1960s,[37] but its unique electrophysiologic actions were not appreciated for many years. The initial electrophysiologic studies, reported by Singh and Vaughan Williams[23] and by Strauss et al,[42] indicated that in all cardiac tissues studied, the drug increased the duration of the action potential in a concentration-dependent fashion. There was a concomitant lengthening of the effective and the absolute refractory period. There was no change in the upstroke velocity of the phase zero of the action potential except when concentrations were 10^{-4} M or greater. Several investigators[49,50] reported the reduction in the upstroke velocity of the action potential by sotalol at high concentrations. Concentration-dependent depression effects on the upstroke velocity of the action potential are shown in Figure 3.

The property of lengthening the cardiac action potential exhibited by sotalol cannot be attributed to its actions as a β blocker. Although some lengthening of the myocardial action potential duration has been reported in rabbits and in humans chronically treated with a number of β blockers,[51,52] the magnitude of such changes has been trivial compared with that found with sotalol or amiodarone. It has not been consistently verified. Therefore, the

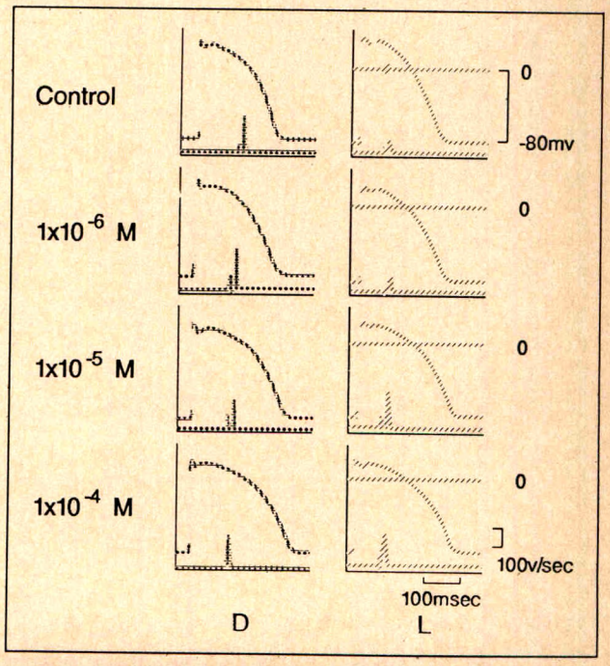


FIGURE 4. Effects of varying concentrations of d- and l-sotalol on the electrophysiologic properties of canine ventricular muscle. Note that the effects of the 2 isomers on the action potential duration are identical. (Adapted from data from *JACC.*[44])

prolongation of the action potential duration induced by sotalol is unlikely to be due to β blockade. This is now supported by our recent observations that the dextroisomer of the drug (nearly devoid of β-blocking property) exerts an identical effect (see Fig. 4) on repolarization, as does l-sotalol.[44] These experimental observations are in accord with the clinical observations: The intravenous injection of the dextroisomer of sotalol in humans had little or no β-blocking effect compared with the racemic mixture; however, the repolarization effects (i.e., on the QTc interval of the electrocardiogram) of the dextroisomer and racemic compound were comparable over the same drug dose range.[53]

Differences between the actions of propranolol, the reference β blocker, and sotalol should be emphasized. For example, Nakaya et al[54] examined the effects of propranolol (0.3 to 30 μM) and sotalol (3 to 300 μM) in canine Purkinje fibers and ventricular muscle fibers using standard microelectrode techniques. Propranolol shortened the action potential duration in Purkinje fibers but had little or no effects in ventricular muscle; in contrast, sotalol produced a concentration-dependent increase in the action potential duration in both tissues. Furthermore, propranolol decreased the maximal rate of rise of the action potential, whereas sotalol had no effect on this parameter except at very high concentrations of the drug, emphasizing the relative selectivity of sotalol for altering repolarization in rather than depolarization of cardiac muscle. The data agree with the observations of Shimatori et al,[55] who examined the effects of 5 different β blockers (including sotalol) on sinoatrial conduction time in isolated blood-perfused canine atria. In contrast to the depressant effects of propranolol, sotalol had no significant effect on sinoatrial conduction.

Effects on membrane currents of sotalol and its stereoisomers: At concentrations equal to or less than 10^{-4} M, Carmeliet[49] found that the main electrophysiologic effect of sotalol and its isomers was to prolong the action potential duration (Fig. 3). At higher concentrations, the action potential duration was shortened and V_{max} significantly reduced because of the inhibition of the tetrodotoxin-sensitive inward sodium ("window") current. The voltage-clamp studies of Carmeliet[49] indicated that lengthening the action potential duration by sotalol may be due to a substantial reduction in the delayed rectifier current (i_K; see Fig. 5) associated with a small decrease in the inward rectifier current (i_{K1}).

These electrophysiologic effects raise 2 theoretical possibilities. First, the lengthening of repolarization will delay the inactivation of the slow-calcium channel (without effect on the magnitude of the peak current), which will produce both a net increase in the intracellular calcium per beat and an increase in myocardial contractility. This is consonant with the findings of Kaumann and Olson[24] and Singh,[33] who reported a positive inotropic effect due to sotalol in feline papillary muscle associated

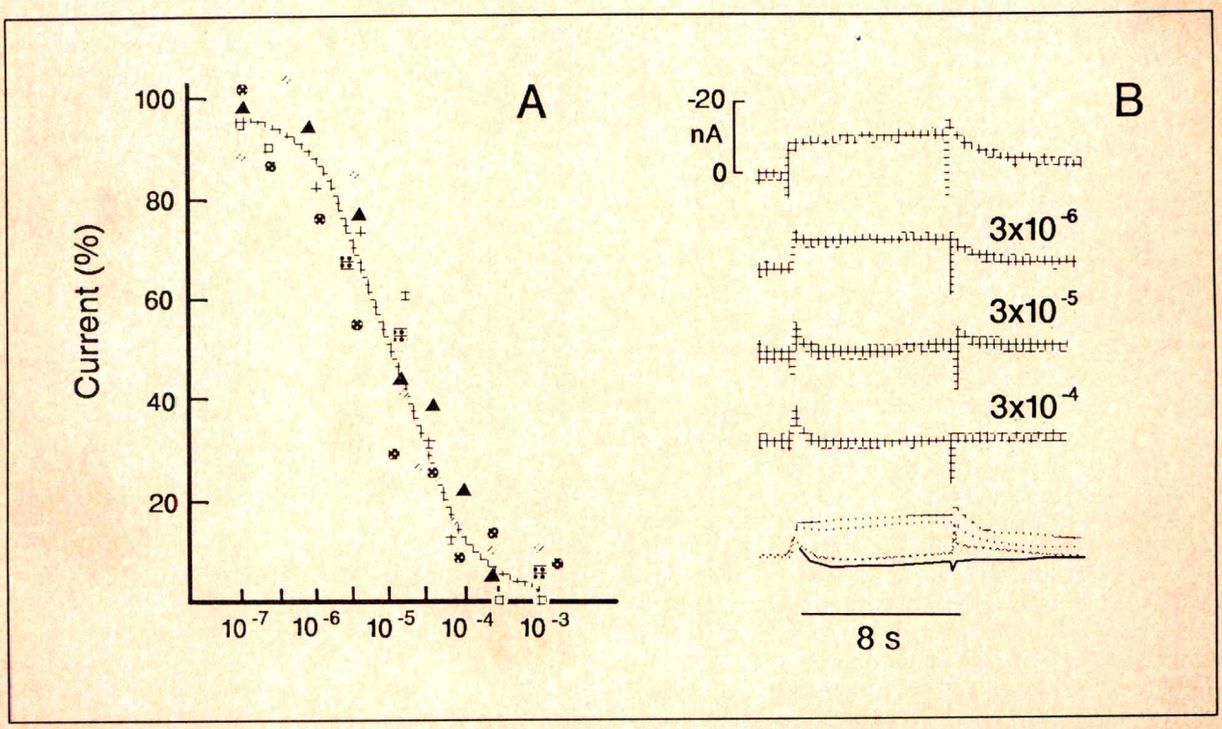


FIGURE 5. ***A*, dose-response relation for the effect of dl-sotalol on the amplitude of the tail current at −50 mV after a conditioning pulse to −20 mV. *Square symbols* indicate mean values obtained for 3 to 5 preparations in which only 1 or up to 3 concentrations were tested. *Other symbols* show individual measurements made in preparations in which the whole range of sotalol concentrations was tested in rabbit Purkinje fibers. *B*, examples of current records obtained in a typical experiment and superimposition of current records (*bottom*) illustrating the progressive inward shift during the clamp and the decrease in tail current on return to the holding potential. (Reproduced with permission from *J Pharmacol Exp Ther.*[49])**

with markedly lengthened action potential duration. In the case of the dextroisomer of sotalol, such an effect is likely to be more pronounced because it will not be attenuated by associated β-receptor blockade. Second, inhibition of the outward K currents by sotalol and its isomers will lengthen the refractory period. Both isomers of sotalol are thus likely to exert antiarrhythmic actions. The differences in the antiarrhythmic effects of the 2 isomers will permit the separation of the net effects due to β blockade and those due, as it were, to "pure" class III electrophysiologic actions.

Clinical electrophysiologic effects of sotalol: The clinical effects of sotalol agree with those found in isolated tissues and in intact animals. Electrophysiologic studies using intravenous drugs have established that sotalol lengthens the monophasic action potential in atria and ventricles in humans[52,56,57] and increases the effective refractory period in atria, ventricle, atrioventricular node and bypass tracts while lengthening the intranodal but not the infranodal conduction time.[26,27,58–61] These properties differ from those of conventional β blockers, which have little or no effect on atrial, ventricular and bypass tract effective refractory periods.[62] The studies of Nademanee et al[27] are in agreement with these findings. Intravenous sotalol lengthened the effective refractory period in atria (+24.6%; $p < 0.01$), atrioventricular node (+24.9%; $p < 0.01$) and ventricle (+14.9%; $p < 0.01$); it significantly lengthened sinus node recovery time QTc and AH but not the HV interval. The effective refractory period of the His-Purkinje system also lengthened after the intravenous administration of sotalol in patients undergoing programmed electrical stimulation of the heart.[63] Very similar overall electrophysiologic data have been reported by Touboul et al[60] and Borggrefe et al,[64] the overall effects being accounted for by summed effects of β blockade and those due to the lengthening of the action potential duration without a change in depolarization.

Comparison of sotalol and propranolol, acute versus chronic effects: Creamer et al[65] compared the acute and the chronic effects of propranolol and sotalol in conventional equiactive β-blocking doses of the 2 antagonists in 8 patients with permanent programmable pacemakers. They found sotalol prolonged the QTc interval by 6.5% after intravenous administration and by 11.5% after 4 weeks of oral therapy. There was no change in the QRS duration, and the entire increase in repolarization was therefore due to a lengthening of the JT interval. The prolongation of the QT and JT intervals was related to plasma concentrations of the drug, but a significant relation was not established in this study. It was interesting that the QT lengthening was greater during chronic therapy despite somewhat lower serum levels of the drug.

After propranolol therapy, there was no change in the QT or JT intervals and, although there was a minor tendency for the QTc to increase after chronic therapy, this did not reach statistical significance. Thus, the data provide further confirmation that the lengthening of the QTc induced by sotalol is not due to its antiadrenergic property. Creamer et al[65] further showed that neither drug affected the pacing threshold of the ventricle after intravenous drug administration.

These findings clearly indicate a combination of β-blocking (class II) and class III actions, a combination that is likely to attribute a broad-spectrum antiarrhythmic effect to sotalol and a side-effect profile that are essentially predictable on the basis of these 2 fundamental actions.

ELECTROPHYSIOLOGIC AND ANTIARRHYTHMIC CORRELATES OF SOTALOL ACTION

There have been numerous experimental[23,33,66–71] and clinical[72–76] reports documenting a broad range of antiarrhythmic effects in the case of dl-sotalol. The spectrum of its effects in arrhythmias is wider than that of conventional β blockers.[23] Other reports in this symposium proceedings discuss the clinical effects from recent investigations. The salient experimental findings relevant to the clinical effects of the drug will be discussed briefly here.

In a model of postmyocardial infarction arrhythmias in conscious dogs, Cobbe et al[68] found that ventricular arrhythmias were prevented by sotalol in 11 of 19 studies (58%) compared with 1 of 14 (7%) with metoprolol, which does not lengthen the action potential duration. The salutary effect of sotalol could be correlated with lengthening the refractory period of the infarct zone, whereas metoprolol had no effect on this parameter, indicating that the antiarrhythmic effect of sotalol was not mediated solely through β blockade. These observations are also consistent with the findings of Marshall et al,[77] who found that giving sotalol intravenously significantly increased the ventricular fibrillation threshold of both normal as well as ischemic myocardium in the anesthetized rat, whereas metoprolol had no effect on the ventricular fibrillation threshold in the normal myocardium and merely prevented the decrease in ventricular fibrillation threshold after coronary artery occlusion. Again, these findings indicate the antifibrillatory and antiarrhythmic actions of sotalol in a variety of animal models, as emphasized by Patterson and Lucchesi.[70] The major effect appears to be mediated through the lengthening of the action potential duration.

Although our data clearly show that the dextroisomer is equipotent with the levoisomer and with the racemic mixture in prolonging the effective refractory period, the data dealing with the antiarrhythmic actions of d-sotalol have been limited.[78]

However, Lynch et al[71] recently found that 8 mg/kg of intravenous cumulative doses of the levo- as well as the dextroisomer suppressed induction of ventricular tachycardia in their conscious-canine ischemic model of sudden death in 50% of the dogs. At this dose, only the l-sotalol exerted an antiadrenergic effect such as lengthening the PR interval of the surface electrocardiogram, but both isomers produced equivalent increases of 15 to 20% in the ventricular effective refractory period.

Culling et al[79] found that the drug prevented ventricular arrhythmias associated with myocardial ischemia and reperfusion in the isolated buffer-perfused model of the

guinea-pig heart. In this preparation, ischemia was produced by reduction of flow to 10% for 30 minutes followed by reperfusion. However, the beneficial effect on the arrhythmia could not be accounted for by alterations in the measured electrophysiologic parameters, such as refractoriness or the time course of the monophasic action potentials. During myocardial ischemia, sotalol has been shown to elevate myocardial pH in the canine heart,[80] and the drug's effect on its so-called class III action is not negated by elevated extracellular potassium.[81]

Finally, there are data that suggest that the antifibrillatory effects of sotalol are not confined to ventricular tissue. Bertrix et al[82] measured the fibrillation threshold in the canine ventricle and atria concurrently with the amplitude and duration of the monophasic action potential, effective refractory period, the conduction time in the contractile fibers, and the fibrillation rate once fibrillation had been triggered. Sotalol increased the fibrillation threshold in association with increases in the duration of the action potential and the effective refractory period. The fibrillation rate slowed but conductive time did not change. The overall changes were more striking in the case of the atria (than in the ventricles) in which vulnerability to fibrillation had been enhanced by acetylcholine (presumably by reversing the cholinergically mediated shortening of the action potential duration and refractoriness). Sotalol antagonized the changes induced by acetylcholine. Experimental data thus provide a compelling basis for the antiarrhythmic and antifibrillatory effects in a broad spectrum of supraventricular and ventricular arrhythmias.

CONCLUSIONS

The experimental and clinical data indicate that sotalol, the prototype of class III antiarrhythmic drugs, exhibits electrophysiologic characteristics that represent summed effects of blocking β receptors and that block potassium channels in a variety of myocardial cells. Therefore, unlike conventional β antagonists, sotalol prolongs the refractory period in the atria, ventricles, His-Purkinje system, and the bypass tracts of the heart in addition to lengthening the refractory period in the atrioventricular node, slowing the heart rate and delaying intranodal conduction, effects that can be related to the block of adrenergic impulse traffic in the heart. The salutary clinical effects of the compound therefore reflect its dual action and emphasize the significance of its major class II as well as its class III actions.

The expanding clinical experience with sotalol as an antiarrhythmic agent is appropriate to the experimental and clinical electrophysiologic effects of this unique β-blocking activity. Unlike conventional β-blocking drugs, dl-sotalol has been found effective in lengthening the anterograde effective refractory period of the bypass tracts in the Wolff-Parkinson-White syndrome and in preventing reinduction of ventricular tachycardia in experimental animals and in humans. These observations, consistent with the additional antiarrhythmic actions of dl-sotalol compared with those of other β blockers, may be due to its propensity to lengthen repolarization and refractoriness in cardiac muscle. Compared with amiodarone, sotalol is a simpler compound electrophysiologically. It exerts similar electrophysiologic actions after intravenous and chronic oral administration. It is therefore likely to be clinically useful in the acute and prophylactic control of a wide variety of supraventricular and ventricular arrhythmias.

REFERENCES

1. Lewis T, Drury AN, Iliescu CC, Wedd AM. Observations relating to the action of quinidine upon the dog's heart: with special reference to its action on clinical fibrillation of the auricles. *Heart 1921;9:55–86.*

2. Lewis R, Drury AN. Revised views of the refractory period in relation to drugs reputed to prolong it, and in relation to circus movement. *Heart 1926;13:95–100.*

3. Weidmann S. Effects of calcium ions and local anesthetics on electrical properties of Purkinje fibers. *J Physiol (Lond) 1955;129:568–582.*

4. Johnson EA. The effect of quinidine, procainamide and pyrilamine on the membrane resting and action potentials of guinea pig ventricular muscle fibers. *J Pharmacol Exp Ther 1956;117:237–246.*

5. Vaughan Williams EM. The mode of action of quinidine on isolated rabbit atria and pacemaker sites in the isolated right atrium of the rabbit. *Br J Pharmacol 1958;13:276–286.*

6. West TC, Amory DW. Single fiber recording of the effects of quinidine at the atrial and pacemaker sites in isolated atrium of the rabbit. *J Pharmacol Exp Ther 1960;130:183–190.*

7. Weidmann S. The effect of the cardiac membrane potential on the rapid availability of the sodium carrier system. *J Physiol (Lond) 1955;127:213–223.*

8. Szekeres L, Vaughan Williams EM. Antifibrillatory action. *J Physiol (Lond) 1962;160:470–482.*

9. Jervell A, Lange-Nielsen F. Congenital deaf-mutism, functional heart disease with prolongation of the QT interval and sudden death. *Am Heart J 1957;54:59–65.*

10. Fraser GR, Froggatt P, James TN. Congenital deafness associated with electrographic abnormalities. *Q J Med 1964;33:361–370.*

11. Schwartz PJ. The idiopatic long Q-T syndrome: progress and questions. *Am Heart J 1985;2:81–90.*

12. Surawicz B, Knoebel S. Long QT. Good, bad or indifferent? *JACC 1984;4:398–413.*

13. Singh BN, Zipes DP. Amiodarone: basic concepts and clinical applications. *Am Heart J 1983;106:787–964.*

14. Vaughan Williams EM. Antiarrhythmic action and the puzzle of perhexiline. *London: Academic Press, 1980;1–35.*

15. Singh BN, ed. Control of Cardiac Arrhythmias by Lengthening Repolarization. *Mount Kisco, New York: Futura Publishing, 1988.*

16. Singh BN. When is QT prolongation anti-arrhythmic and when is it proarrhythmic? *Am J Cardiol 1989;63:867–869.*

17. Alessie M, Lammers WJEP, Bonke FI, Hollen J. Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation. In: Zipes DP, Jalife J, eds. Cardiac Electrophysiology and Arrhythmias. *New York: Grune & Stratton, 1985;267–275.*

18. Josephson MA, Singh BN. Hemodynamic effects of class III anti-arrhythmic agents. In: Singh BN, ed. Control of Cardiac Arrhythmias by Lengthening Repolarization. *Mount Kisco, New York: Futura Publishing, 1988;153–174.*

19. Platou ES. Class III antiarrhythmic action with special reference to the electrophysiological and hemodynamic effects of melperone. *Doctoral Thesis, Institute of Medical Biology, University of Tromso, Tromso, Norway, 1982.*

20. Francis GS. Development of arrhythmias in patients with congestive failure: pathophysiology, prevalence and prognosis. *Am J Cardiol 1986;57:3B–10B.*

21. Kavaler F. Membrane depolarizations as a cause of tension development in mammalian cardiac muscle. *Am J Physiol 1958;197:968–976.*

22. Morad M, Trautwein W. The effect of the duration of the action potential on contraction in the mammalian heart muscle. *Pflügers Arch 1968;229:66–72.*

23. Singh BN, Vaughan Williams EM. A third class of antiarrhythmic action: effects on atrial and ventricular intracellular potentials, and other pharmacological actions on cardiac muscle of MJ1999 and AH 3676. *Br J Pharmacol 1970;39:675–689.*

24. Kaumann AJ, Olson CB. Temporal relationship between longlasting after contractions and action potentials in cat papillary muscles. *Science 1968;161:293–298.*

25. Brooks H, Banas J, Meister S, Szucs M, Dalen J, Dexter L. Sotalol-induced beta-blockade in cardiac patients. *Circulation 1970;42:99–109.*

26. Senges J, Lengfelder W, Jauernig R, Czyfan E, Brachmann J, Rizos I, Cobbe S, Kubler W. Electrophysiologic testing of therapy with sotalol for sustained ventricular tachycardia. *Circulation 1984;69:577–583.*

27. Nademanee K, Feld G, Hendrickson JA, Singh PN, Singh BN. Electrophysiologic and antiarrhythmic effects of sotalol in patients with life-threatening ventricular tachyarrhythmias. *Circulation 1985;72:555–563.*

28. Freedberg AS, Papp JG, Vaughan Williams EM. The effect of altered thyroid state on atrial intracellular potentials. *J Physiol (Lond) 1970;207:357–*

370.
29. Johnson PN, Freedberg AS, Marshall JM. Action of thyroid hormone on the transmembrane potentials from sino-atrial node cells and atrial cells in isolated atria of rabbits. *Cardiology 1973;58:273–289.*
30. Arnsdorf MF, Childers RW. Atrial electrophysiology in experimental hypothyroidism in rabbits. *Circ Res 1970;26:575–581.*
31. Olsson BE, Cotoi S, Varnauskus E. Monophasic action potential and sinus rhythm stability after conversion of atrial fibrillation. *Acta Med Scand 1971; 190:381–390.*
32. Singh BN. Amiodarone: historical development and pharmacologic profile. *Am Heart J 1983;106:788–797.*
33. Singh BN. A study of the pharmacological actions of certain drugs and hormones with a particular reference to cardiac muscle. *D. Phil. Thesis, University of Oxford, England, 1971.*
34. Cobbe SM, Hoffman E, Ritzenhoff A, Brachmann J, Kubler W, Senges J. Action of sotalol on potential re-entrant pathways and ventricular tachyarrhythmias in conscious dogs in the late post myocardial infarction phase. *Circulation 1973;68:865–871.*
35. Singh BN, Vaughan Williams EM. The effect of amiodarone, a new antianginal drug, on cardiac muscle. *Br J Pharmacol 1970;39:657–663.*
36. Aberg G, Dzedin T, Lundholm L, Olsson L, Svedmyr N. A comparative study of some cardiovascular effects of sotalol (MJ 1999) and propranolol. *Life Sci 1969;8:353–365.*
37. Lish PN, Weikel JH, Dungan KW. Pharmacological and toxicological properties of two new beta-adrenergic receptor antagonists. *J Pharmacol Exp Ther 1965;149:161–168.*
38. Blinks JR. Evaluation of the cardiac effects of several beta-adrenergic blocking agents. *Ann NY Acad Sci 1967;139:673–690.*
39. Parmley WW, Rabinowitz B, Chuck L, Bonorris G, Katz JP. Comparative effects of sotalol and propranolol on contractility of papillary muscles and adenyl cyclase activity of myocardial extracts of cat. *J Clin Pharmacol 1972;12:127–136.*
40. Gomoll AW, Braunwald E. Comparative effects of sotalol and propranolol on myocardial contractility. *Arch Int Pharmacodyn 1973;205:338–354.*
41. Goldstein RE, Hall CA, Epstein SE. Comparison of relative inotropic and chronotropic effects of propranolol, practolol and sotalol. *Chest 1973;64:619–627.*
42. Strauss HC, Bigger JT, Hoffman BF. Electrophysiological and beta-receptor blocking effects of MJ 1999 on dog and rabbit cardiac tissue. *Circ Res 1970;26:661–670.*
43. Lewis MJ, Grey AC, Henderson AH. Inotropic beta-blocking potency (pA_2) and partial agonist activity of propranolol, practolol, sotalol and acebutolol. *Eur J Pharmacol 1983;86:71–76.*
44. Kato R, Yabek S, Ikeda N, Kannan R, Singh BN. Electrophysiologic effects of dextro- and levo-isomers of sotalol in isolated cardiac muscle and their in vivo pharmacokinetics. *JACC 1986;7:116–125.*
45. Barrett AM, Carter J. Comparative chronotropic activity of beta adrenoceptor antagonists. *Br J Pharmacol 1970;40:373–380.*
46. Kaumann AJ, Blinks JR. Beta-adrenoceptor blocking agents as partial agonists in isolated heart muscle. Part 1. *Naunyn Schmiedebergs Arch Pharmacol 1980;311:205–215.*
47. Kaumann AJ, Blinks JR. Beta-adrenoceptor blocking agents as partial agonists in isolated heart muscle. Part 2. *Naunyn Schmiedebergs Arch Pharmacol 1980;311:237–250.*
48. Kaumann AJ, McKerny TK, Gilmour DP, Blinks JR. Comparative assessment of beta-adrenoceptor blocking agents as simple competitive antagonists in isolated heart muscle. *Naunyn Schmiedebergs Arch Pharmacol 1980;311:219–228.*
49. Carmeliet E. Electrophysiologic and voltage clamp analysis of sotalol effects in cardiac muscle and Purkinje fibers. *J Pharmacol Exp Ther 1985;232:3:817–825.*
50. Ban T, Sada S, Takahashi Y, Sada SH, Fujita T. Effects of para-substituted beta-adrenoceptor blocking agents and methyl-substituted phenoxypropanolamine derivatives on maximum upstroke velocity of action potential in guinea-pig papillary muscles. *Naunyn Schmiedebergs Arch Pharmacol 1985;329:77–85.*
51. Raine AEG, Vaughan Williams EM. Adaptational responses to prolonged beta-adrenoceptor blockade in adult rabbits. *Br J Pharmacol 1980;70:205–215.*
52. Edvardsson N, Olsson B. Effects of acute and chronic beta-receptor blockade on ventricular repolarization in man. *Br Heart J 1981;45:628–636.*
53. Johnston GD, Finch MB, McNeill JA, Shanks RG. A comparison of the cardiovascular effects of (+)-sotalol and (±)-sotalol following intravenous administration in normal volunteers. *Br J Clin Pharmacol 1987;20:507–510.*
54. Nakaya H, Kimura S, Nakao Y, Kanno M. Effects of nipradilol (K-351) on the electrophysiologic properties of canine cardiac tissues: comparison with propranolol and sotalol. *Eur J Pharmacol 1984;104:335–344.*
55. Shimatori M, Kobayashi M, Chiba S. Comparative study of five beta-adrenoceptor blocking agents on sino-atrial conduction time in isolated blood-perfused canine atria. *Arch Int Pharmacodyn 1985;274:240–252.*
56. Edvardsson N, Hirsch L, Emmanuelsson H, Ponten J, Olsson SB. Sotalol-induced delayed ventricular repolarization in man. *Eur Heart J 1980;1:335–340.*
57. Echt DS, Berte LE, Clusin WT, Samuelssoywn RG, Harrison DC, Mason JW. Prolongation of the human cardiac monophasic action potential by sotalol. *Am J Cardiol 1982;50:1082–1086.*
58. Ward DE, Camm AJ, Spurrel RAJ. The acute cardiac electrophysiological effects of intravenous sotalol hydrochloride. *Clin Cardiol 1979;2:185–190.*
59. Nathan AW, Hellerstrand KJ, Bextan RS, Ward DE, Spurrell RAJ, Camm AJ. Electrophysiological effects of sotalol—just another beta-blocker? *Br Heart J 1982;47:515–520.*
60. Touboul P, Atallah G, Kirkorian G, Lamaud M, Moleur P. Clinical electrophysiology of intravenous sotalol, a beta-blocking drug with Class III antiarrhythmic properties. *Am Heart J 1984;107:888–895.*
61. Dumoulin P, Weissenburger J, Poirier JM, Rosensztajn L, Gallet B, Jaillon P, Tetard D, Cheymol G, Valty J. Étude des effects electrophysiologiques du sotalol intraveineux. Relation avec les concentrations plasmatiques. *Arch Mal Coeur Vaisseaux 1985;78:562–568.*
62. Horowitz LN, Josephson ME, Kastor JA. Intracardiac electrophysiologic studies as a method for the optimization of drug therapy in chronic ventricular arrhythmias. *Prog Cardiovasc Dis 1980;23:81–98.*
63. Nademanee K, Feld G, Noll E, Hendrickson JA, Singh BN. Effects of sotalol, class III antiarrhythmic agent on conduction and refractoriness of the His-Purkinje system in man. *JACC 1985;4:38–45.*
64. Borggrefe M, Breithardt G, Seipel L. Sotalol-induced distal block (abstr). *Circulation 1983;7:suppl II:II-271.*
65. Creamer JE, Nathan AW, Shennan A, Camm AJ. Acute and chronic effects of sotalol and propranolol on ventricular repolarization using constant rate-pacing. *Am J Cardiol 1986;57:1092–1096.*
66. Schmid JR, Hanna C. A comparison of the antiarrhythmic actions of two new synthetic compounds, iproveratril and MJ1999, with quinidine and pronethalol. *J Pharmacol Exp Ther 1967;156:331–338.*
67. Kaumann A, Aramendia P. Prevention of ventricular fibrillation induced by coronary ligation. *J Pharmacol Exp Ther 1968;164:326–332.*
68. Cobbe SM, Hoffman E, Rienhoff A, Brachmann J, Kubler W, Senges J. Action of sotalol on potential re-entrant pathways and ventricular tachyarrhythmias in conscious dogs in the late post myocardial infarction phase. *Circulation 1963;68:865–871.*
69. Patterson E, Lynch JJ, Lucchesi BR. The antiarrhythmic and antifibrillatory actions of the beta-adrenergic receptor antagonist, dl-sotalol. *J Pharmacol Exp Ther 1984;230:519–526.*
70. Patterson E, Lucchesi BR. Antifibrillatory properties of the beta-adrenergic receptor antagonists, nadolol, sotalol, atenolol and propranolol in the anesthetized dog and rabbit cardiac tissue. *Pharmacology 1984;28:121–129.*
71. Lynch JJ, Wilber DJ, Montgomery DG, Hsieh TM, Patterson E, Lucchesi BR. Antiarrhythmic and fibrillatory actions of levo- and dextro-rotatory isomers of sotalol. *J Cardiovasc Pharmacol 1984;6:1132–1141.*
72. Fogelman F, Lightman SL, Sillett RW, McNicol MW. The treatment of cardiac arrhythmias with sotalol. *Eur J Clin Pharmacol 1972;5:72–76.*
73. Myburgh DP, Goldman AP, Cartoon J, Schamroth JM. The efficacy of sotalol in suppressing ventricular ectopic beats. *S Afr Med J 1979;56:295–302.*
74. Prakash R, Parmley WW, Allen HN, Matloff JM. Effects of sotalol on clinical arrhythmias. *Am J Cardiol 1972;29:397–402.*
75. Rizos I, Senges J, Jauernig R, Lengfelder W, Czygan E, Brachmann J, Kubler S. Differential effects of sotalol and metoprolol on induction of paroxysmal supraventricular tachycardia. *Am J Cardiol 1984;53:1022–1029.*
76. Simon A, Berman E. Long-term sotalol therapy in patients with arrhythmias. *J Clin Pharmacol 1979;19:547–554.*
77. Marshall RJ, Muir AW, Winslow E. Effects of antiarrhythmic drugs on ventricular fibrillation thresholds of normal and ischemic myocardium on the anesthetized rat. *Br J Pharmacol 1983;78:165–171.*
78. Somani P, Watson DL. Antiarrhythmic activity of the dextro- and levo-rotatory isomers of 4-(2-isopropylamino-1-hydroxyethyl) methanesulfonanilide (MJ1999). *J Pharmacol Exp Ther 1968;164:317–325.*
79. Culling W, Penny WJ, Sheridan DJ. Effects of sotalol on arrhythmias and electrophysiology during myocardial ischemia and reperfusion. *Cardiovasc Res 1984;18:397–404.*
80. Izumi T, Sakai K, Abiko Y. Effects of sotalol on ischemic myocardial pH in the dog heart. *Arch Pharmacol 1982;318:340–343.*
81. Cobbe SM, Manley BS. Effects of elevated extracellular potassium concentrations on the Class III antiarrhythmic action of sotalol. *Cardiovasc Res 1985;19:69–75.*
82. Bertrix L, Timour-Chah Q, Lang J, Lakhal M, Faucon G. Protection against ventricular and atrial fibrillation by sotalol. *Cardiovasc Res 1986;20:358–363.*

Pharmacology, Pharmacodynamics and Pharmacokinetics of Sotalol

Michael J. Antonaccio, BS, PhD, and Allen Gomoll, BS, PhD

Sotalol is a nonselective, water-soluble β-adrenoceptor antagonist with no membrane-stablizing activity or intrinsic sympathomimetic activity. Sotalol is, essentially, completely absorbed and is not metabolized. Consequently, bioavailability is close to 100%. Age and food have slight but unimportant effects on bioavailability. C_{max} of sotalol is 2 to 3 hours with a $t_{1/2}$ between 7 and 15 hours. Excretion of sotalol is primarily through the kidneys, with no metabolism by liver and no first-pass effect. Therefore, sotalol plasma levels and half-life are directly related to creatinine clearance and glomerular filtration rate. Appropriate dose adjustments must be made for patients with impaired renal function or increased renal blood flow, as in pregnancy.

The β-adrenoceptor antagonistic effects of sotalol are directly related to plasma levels, which, in turn, are directly related to dose. However, the β-adrenoceptor antagonism $t_{1/2}$ is longer than the sotalol plasma $t_{1/2}$.

As a consequence of its ability to prolong the action potential duration, sotalol also increases cardiac contractility in isolated ventricular, but not atrial, preparations by 20 to 40%. This positive inotropic effect is not blocked by β or α blockade or reserpine pretreatment and seems to be related to sotalol's effects on cardiac ionic currents. Like the effects of sotalol on action potential duration, the positive inotropic effects are inversely proportional to rate.

The hemodynamics of sotalol indicate a relative lack of direct cardiac depressant activity in both animals and humans. The typical hemodynamic effects of sotalol in normotensive humans, even with depressed myocardial function, are a reduction in heart rate with little or no change in blood pressure, a reduction in cardiac output with no change in stroke volume, and little or no change in pulmonary wedge pressure and left ventricular end-diastolic pressure or volume, and little or no change in ejection fraction either at rest or during exercise.

(Am J Cardiol 1990;65:12A–21A)

From the Bristol-Myers Pharmaceutical Research and Development Division, Wallingford, Connecticut.

Address for reprints: Michael J. Antonaccio, PhD, Bristol-Myers Pharmaceutical Research and Development Division, 5 Research Parkway, Wallingford, Connecticut 06492-7660.

Sotalol was discovered in 1960, before propranolol, but its unique properties as an antiarrhythmic agent with both class II β-adrenoceptor antagonism and the class III ability to prolong cardiac repolarization were not fully realized until relatively recently. Because the electrophysiologic and antiarrhythmic effects of sotalol will be emphasized elsewhere in this symposium, this discussion will focus on the pharmacodynamics and hemodynamics of this drug.

PHARMACOKINETICS

The absorption of sotalol is virtually complete. Comparisons of intravenous (i.v.) and oral sotalol in both animals and humans indicate that the absolute bioavailability of sotalol ranges from 89 to 102%[1–3] (Bristol-Myers Company, unpublished observations). Sotalol is absorbed at a fairly rapid rate, with peak levels generally observed 2 to 4 hours after oral administration (Fig. 1).[1,4,5] In mice and rats (Bristol-Myers Company, unpublished observations), and dogs[1] and humans,[5] plasma levels of sotalol are linearly proportional to dose (Fig. 2). In humans, in doses ranging from 80 to 640 mg, C_{max} and the area under the curve were directly proportional to dose, whereas T_{max} and half-life values were not, both after a single dose and at steady state (Bristol-Myers Company, unpublished observations).

Sotalol is apparently not metabolized, since no metabolites have been detected in plasma or urine from animals or humans.[6–9] Labeled metabolites of sotalol were detected in the bile of dogs but accounted for less than 1% of the administered dose.[1] In patients with hepatic impairment, sotalol pharmacokinetics were similar to those in normal subjects.[10] In addition, dl-sotalol was excreted equally in urine as d- and l-sotalol, indicating a lack of isomerization and no difference in clearance of the enantiomers (Bristol-Myers Company, unpublished observations). The lack of metabolism and the total absorption of sotalol account for its 100% bioavailability.

Most amounts of sotalol are excreted in urine. In rats, 73% of a single oral dose of 400 mg/kg was excreted in urine (Bristol-Myers Company, unpublished observations). In dogs, urinary excretion after oral or i.v. sotalol administration was 89 and 91% of the dose, respectively.[1] In another study in which oral doses of 0.1, 1.6 and 50 mg/kg of sotalol were administered, urinary excretion of unchanged drug was 89, 82 and 93% of the dose, respectively, indicating that the extent of urinary excretion is independent of dose (Bristol-Myers Company, unpublished observations). In humans, the primary route of sotalol elimination is also by renal excretion. After oral

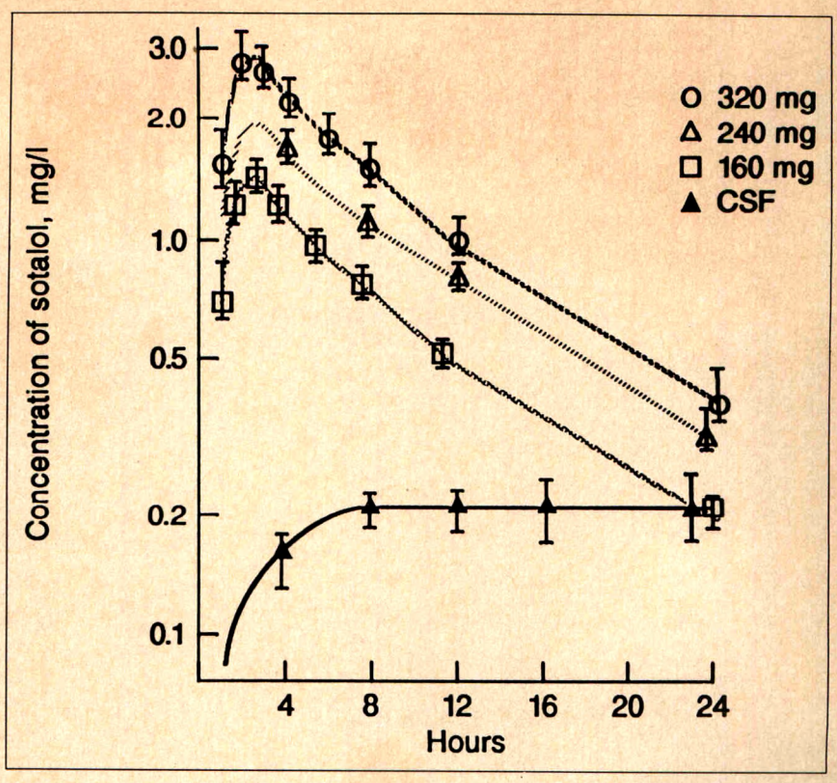


FIGURE 1. Plasma and cerebrospinal fluid (CSF) levels of sotalol in humans. (Adapted from *Curr Ther Res.*[5])

administration of sotalol, in doses ranging from 5 to 160 mg, the mean urinary recovery of sotalol was 80.1% of the dose, whereas 12.5% was in feces. After i.v. administration, 76.6% of the dose was recovered in urine and only 1.0% in feces (Bristol-Myers Company, unpublished observations).

Because the clearance of sotalol is primarily by renal excretion, positive correlations between sotalol plasma levels and renal function have been consistently demonstrated. Sundquist et al[11] observed a slower elimination rate of sotalol after a single oral dose of 160 mg as the serum creatinine concentration increased. Berglund et al[12] demonstrated a linear relation between the elimination rate constant, as well as plasma clearance of sotalol and glomerular filtration rate in hypertensive patients. In normal subjects, both sotalol plasma clearance and renal clearance were linearly correlated with creatinine clearance (Fig. 3).[5] In end-stage renal failure, it is not surprising, therefore, to observe a dramatic increase in the half-life of sotalol of 41.3 hours compared with a 5.2-hour half-life in normal subjects with no change in peak plasma levels.[7] In these uremic patients, only 9% of the sotalol dose was excreted in urine over 48 hours compared with 61% in normal patients. Hemodialysis can result in a 20% increase of the sotalol plasma decay rate.

In elderly patients, the half-life, but not peak plasma level, of sotalol was modestly increased from 7.1 to 11.4 hours as a consequence of a decrease in renal clearance of the drug, requiring no dosage adjustment in these patients.[13] An increase in sotalol clearance in pregnant women was related to the increase in renal blood flow known to occur in pregnancy.[3] Clearly, patients with renal insufficiency or failure require lengthening of the dosage interval to 48 hours or more to compensate for the longer half-life of sotalol in these patients. However, the

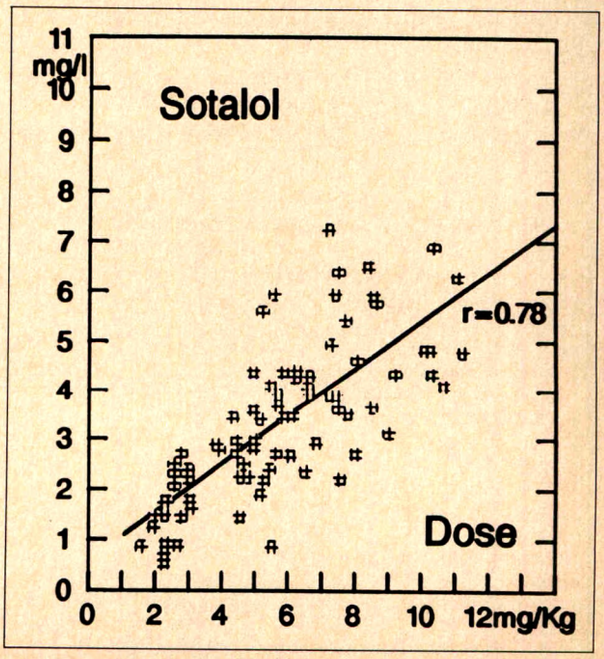


FIGURE 2. Plasma levels after various oral doses of sotalol. (Adapted from *Curr Ther Res.*[5])

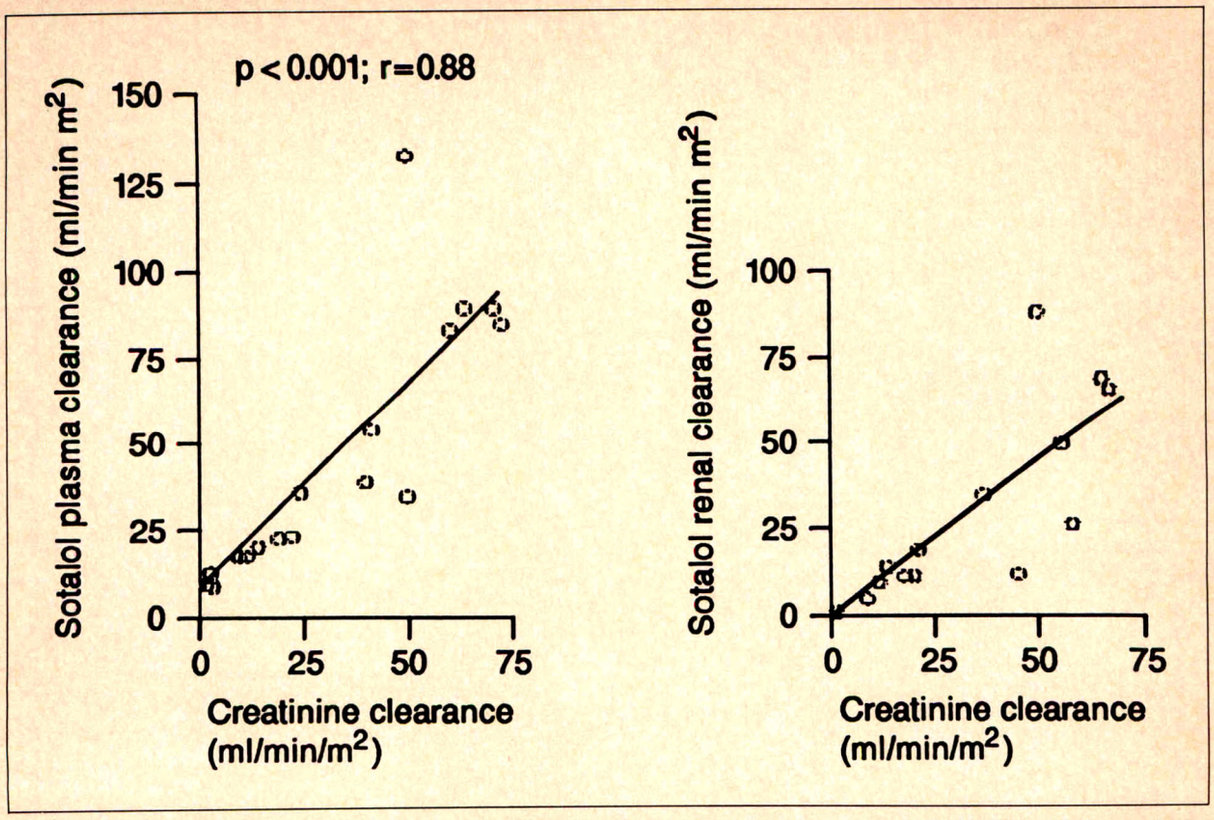


FIGURE 3. ***Left,*** **linear regression of sotalol plasma clearance/creatinine clearance. Approximately 77% of sotalol plasma clearance correlates with creatinine clearance, indicating a small degree of nonrenal elimination.** ***Right,*** **linear regression of renal clearance/creatinine clearance indicating that sotalol is eliminated in a manner similar to creatinine, namely glomerular filtration. (Adapted from** ***Clin Pharmacol Ther.***[6]**)**

bioavailability and pharmacokinetics of sotalol are not significantly altered by simultaneous hydrochlorothiazide therapy.[14]

Plasma clearance of propranolol and sotalol were compared in 68 patients with hypertension or angina pectoris using both antipyrine clearance and cytochrome P-450 content as a measure of the hepatic drug-metabolizing enzyme system.[10] Propranolol elimination from plasma was directly related to both antipyrine clearance and cytochrome P-450 levels, whereas sotalol plasma clearance was not related to hepatic function. The plasma clearance rate of propranolol, but not sotalol, was increased by alcohol ingestion and related to blood alcohol content.[15] Since alcohol stimulated hepatic drug-metabolizing enzymes, this is further evidence that hepatic function can alter propranolol but not sotalol clearance.

Large volumes of fluid delay but do not affect the extent of sotalol absorption. Food slightly decreases the availability of the drug but does not require any alteration in dosage.[16]

A summary of the clinical pharmacokinetic profile of sotalol is listed in Table I, and a comparison of the pharmacokinetic characteristics of sotalol in comparison with several other β-adrenoceptor antagonists is listed in Table II.

TABLE I Summary of Clinical Pharmacokinetic Profile of Sotalol*

Absorption rate	T_{max} of 2 to 3 hours
Extent of absorption	>90% of dose
Extent of bioavailability	~100% of dose
Binding to plasma protein	0%
Apparent volume of distribution	1.6 to 2.4 l/kg
Elimination renal (unchanged)	~90%
Biotransformation	0%
Apparent plasma half-life	15 (7 to 18) hours
Pattern of elimination kinetics	First order
Kinetic model applicable	Open 2-compartment
Metabolites	None detected
Steady-state/dose ratio	Twofold variation
Special features	Accumulation in renal failure Kinetics not affected by liver function

* Adapted from *Curr Ther Res.*[5]
Reproduced with permission from *Cardiovasc Drug Rev 1988;6:239–263.*

DOSAGE AND ADMINISTRATION

Sotalol is available as an i.v. as well as oral formulation. In the treatment of supraventricular and ventricular arrhythmias, doses of the drug between 0.2 and 1.5 mg/kg given intravenously have been used without problems in patients with normal as well as depressed ejection

TABLE II Pharmacokinetic Characteristics of Various Beta-Adrenoceptor Antagonists*

Drug	Rate of Absorption T_{max} (H)	Extent of Absorption (% of dose)	Extent of Bioavailability (% of dose)	Plasma Protein Binding (% bound)	Distribution Ratio n-Octanol/Water at pH 7.0	Half-Life (hours)
Sotalol	2 to 3	>90	~100	0	<0.02	10 to 15
Alprenolol	1 to 2	>90	~10	85	3.1	2
Atenolol	2 to 4	~50 (40 to 65)	~50 (40 to 65)	3	<0.02	6 to 8
Metoprolol	1 to 2	>95	~40 (20 to 60)	12	0.2	3
Oxprenolol	1 to 2	~80 (70 to 95)	~40 (20 to 75)	78	0.7	2
Pindolol	1 to 2	>90	~85	57	0.2	2 to 4
Propranolol	1 to 3	>90	~30	80 to 95	4.3	3 to 5
Timolol	1 to 4	~70	~55	80	0.3	4

* Adapted from Curr Ther Res.[5]
Reproduced with permission from *Cardiovasc Drug Rev 1988;6:239–263.*

fractions. As in the case of all i.v. β blockers, slow administration is recommended; for high-risk patients (i.e., those with acute myocardial infarction), careful monitoring of hemodynamic or electrocardiographic changes is recommended.

The minimal clinically effective dosage for orally administered sotalol in arrhythmia treatment is likely to be either 80 mg once daily or 40 mg twice daily, taken before food. Available evidence suggests that 160 mg once daily is probably the appropriate antiarrhythmic dosage, particularly for supraventricular arrhythmias. Although this dosage may be increased every 3 to 4 days to a maximum of 480 mg/day, the efficacy and safety of daily doses greater than this has not been critically evaluated. Furthermore, doses greater than 640 mg/day should be used in conjunction with careful monitoring of electrocardiographic changes, serum drug concentrations, and the possibility of concomitant hypokalemia (particularly when diuretics are used concomitantly). In the treatment of hypertension and angina pectoris, sotalol should initially be given as either 80 or 160 mg once or twice daily. Should dosage titration be necessary after an adequate trial of the drug (7 to 10 days), the sotalol dose may be increased by an additional 40 to 160 mg; further increments may be given, if necessary, at intervals of 2 or more weeks.

In patients with reduced renal function, a careful adjustment of drug dose and dosing interval is necessary. In cases of moderate impairment of renal function, the initial dose should not exceed 160 mg/day and subsequent dose adjustment should be made on the basis of clinical response and serum drug concentrations. In patients with severely compromised renal function (e.g., glomerular filtration rate reduced below 25 ml/min/1.73 m^2), sotalol should be avoided or be used with frequent monitoring of serum drug concentrations and the electrocardiogram.

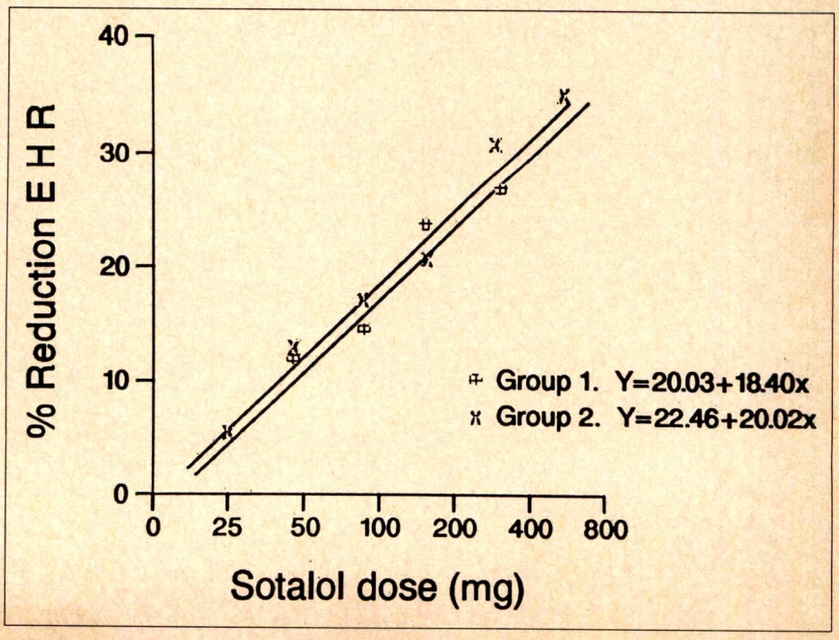


FIGURE 4. Percentage reduction in exercise heart rate (EHR) after oral sotalol. Group 1 consisted of 5 patients who received each dose of sotalol. Group 2 consisted of 5 different subjects who received each dose of sotalol. (Adapted from *Eur J Clin Pharmacol.*[20])

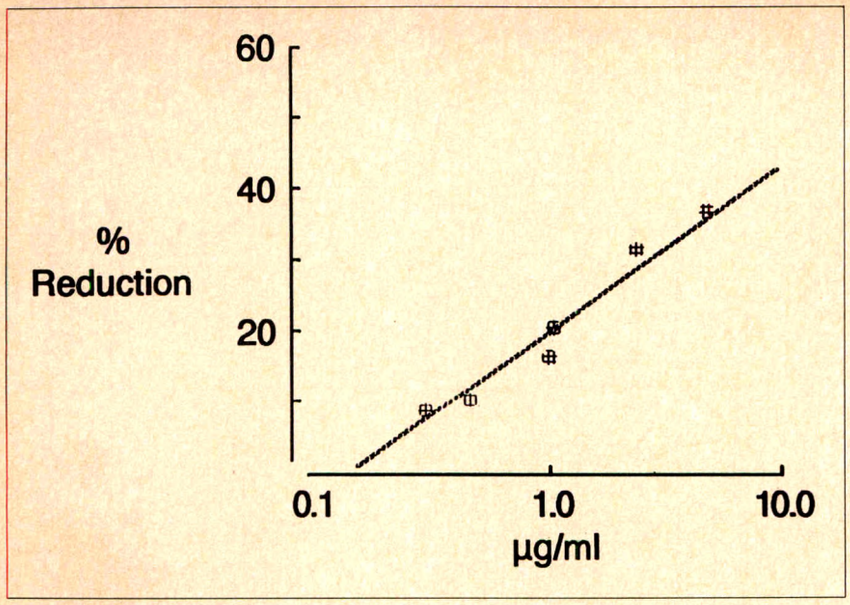


FIGURE 5. Correlation of mean percent reduction of exercise heart rate during exercise (*ordinate*) with the logarithm of the mean plasma sotalol concentration (*abscissa*). (Adpted from *Eur J Clin Pharmacol.*[20])

PHARMACODYNAMICS

In dogs, positive correlations of sotalol plasma levels with inhibition of isoproterenol tachycardia and reduction in heart rate, atrioventricular conduction, as well as atrial and ventricular refractoriness have been reported.[17–19] The relation between β blockade and time after sotalol in dogs indicated that although the canine plasma sotalol concentration correlated significantly with β blockade, plasma concentrations declined at a first-order rate, whereas β blockade declined at a zero-order rate. In humans, the oral administration of sotalol to normal subjects (25 to 800 mg) produced a dose-related reduction to exercise-induced tachycardia[20] (Fig. 4). In addition, the percent reduction of heart rate during exercise was significantly correlated with the logarithm of plasma sotalol concentrations (Fig. 5). Significant reductions in heart rate during exercise were still apparent 24 to 72 hours after administration of a 400-mg dose of sotalol. Similar results have also been reported by Harron et al.[21] Ishizaki et al[13] evaluated the percent inhibition of exercise tachycardia, as well as the absolute reduction of heart rate during exercise in relation to the logarithm of sotalol plasma levels in normal subjects. They found that the best relation to β blockade was that to absolute reduction of exercise heart rate. As in dogs, they found that β blockade with sotalol declined at a zero-order rate, whereas plasma levels declined at a first-order rate, indicating that the pharmacologic effect of sotalol lasts longer than its half-life. These investigators[13] also found that the plasma level of sotalol, although related to β blockade, was not correlated with the blood pressure–reducing effect. Other studies have also demonstrated a lack of correlation between the plasma level of sotalol and its antihypertensive effect.[11,12]

TABLE III Characteristics of Beta-Adrenoreceptor Antagonists

Drug	Potency (Propranolol = 1)	Local Anesthetic Activity	ISA	Cardio-selectivity
Sotalol	0.3	0	0	—
Nadolol	0.5	0	0	—
Timolol	5 to 10	0	0	—
Bunolol	50	0	0	—
Atenolol	1	0	0	+
Metoprolol	0.5 to 2	±	0	+
Propranolol	1	++	0	—
Labetalol	0.3	+	±	—
Acebutolol	0.3	+	+	+
Alprenolol	0.3 to 1	+	++	—
Oxprenolol	0.5 to 1	+	++	—
Pindolol	5 to 10	±	+++	—

ISA = intrinsic sympathomimetic activity. + = slight effect; ++ = moderate effect; +++ = marked effect; 0 = no effect.

Pharmacology: Unlike all other available β-adrenoceptor antagonists (Table III), which are aryloxypropanolamines, sotalol is a methanesulfonamide-substituted phenethanolamine (Fig. 6). Sotalol is a nonselective, competitive antagonist of β adrenoceptors, devoid of membrane-stabilizing (except at very high drug concentrations) or intrinsic sympathomimetic activity. No other

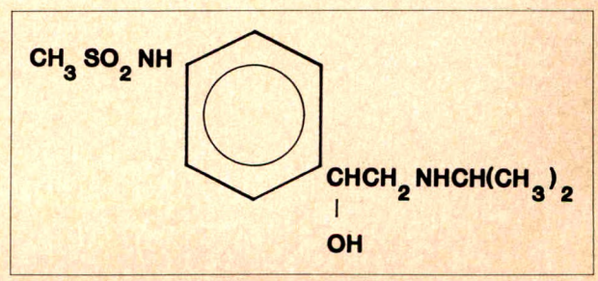


FIGURE 6. Chemical structure of sotalol.

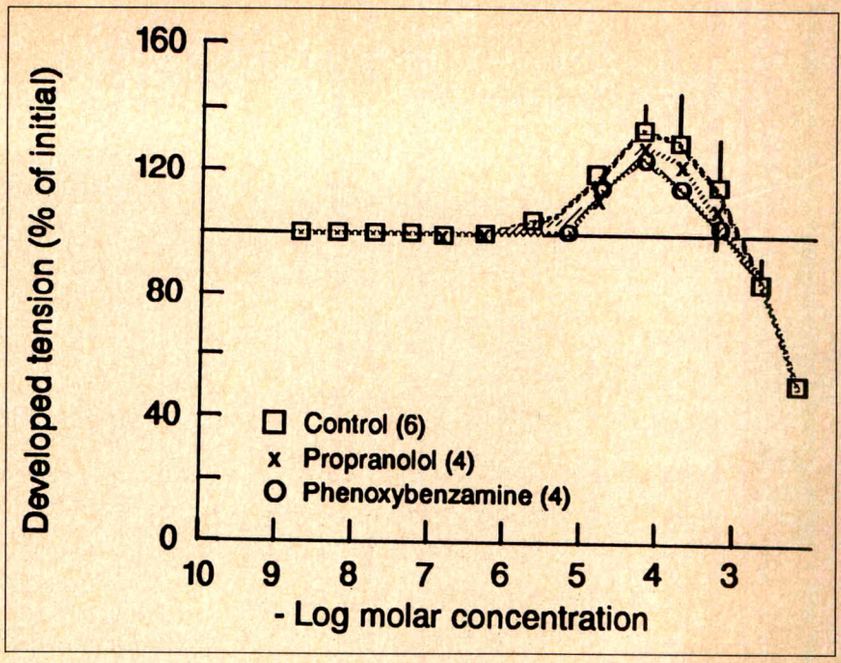


FIGURE 7. Positive inotropic effect of various concentrations of sotalol alone or in the presence of 10^{-6} M propranolol or 5×10^{-6} M phenoxybenzamine, the latter also having been taken from reserpine-treated kittens. (Adapted from *Naumyn Schmiedebergs Arch Pharmacol.*[34])

important receptor-blocking activity of the drug has been reported. Although sotalol also has the ability to increase the action potential duration and repolarization time of cardiac muscle, the antiarrhythmic and relevant electrophysiologic correlates of the drug will not be dealt with here since this is the subject of another article in this issue.[22]

Beta-adrenoceptor antagonism: Racemic sotalol displaced ^{3}H-dihydralprenolol from guinea-pig heart and lung with IC_{50} values of 0.80 and 0.77, respectively, indicating a lack of selectivity. Propranolol was 111 and 126 times as potent in heart and lung, respectively (Bristol-Myers Company, unpublished observations). The l-isomer of sotalol was 250 and 14 times more potent than the d-isomer in heart and lung, respectively.

In a variety of isolated tissues, including the rat uterine horn,[23,24] rabbit and kitten right atria,[24,25] rabbit and kitten papillary muscle,[26,27] and perfused feline heart,[25] sotalol was found to have little or no direct effect while producing rightward shifts of dose-response curves to β-adrenoceptor agonists. Quantitative estimates of the β antagonism of sotalol and propranolol yielded β-blocking potency (pA_2) values of 6.4 (4×10^{-7} M) for sotalol and 8.7 (2×10^{-9} M) for propranolol.

In whole animals, sotalol also produced competitive blockade of both β_1 and β_2 adrenoceptors. In anesthetized dogs, the threshold blocking dose of sotalol against isoproterenol-induced tachycardia was 78 μg/kg administered intravenously, with maximal blockade occurring at 625 μg/kg intravenously.[25] In conscious rats, the oral dose producing 50% inhibition of isoproterenol-induced tachycardia was 6.3 and 15.5 mg/kg after 0.5 and 30 hours post-treatment.[17] In various preparations of anesthetized dogs, propranolol was found to be between 4 and 10 times as potent as sotalol.[28,29] The calculated pA_2 values for racemic sotalol in anesthetized dogs was 6.6 for both heart rate and diastolic blood pressure changes induced by isoproterenol, whereas they were 5.4 and 5.5 for d-sotalol and 6.8 and 7.1 for l-sotalol, respectively.[30] The large differences in the in vitro and in vivo potencies of sotalol compared with propranolol are undoubtedly related to the total bioavailability of sotalol compared with the poor bioavailability of propranolol and other agents.

The relative characteristics of sotalol to other β-adrenoceptor antagonists with respect to potency, local anesthetic (membrane stabilizing) activity, intrinsic sympathomimetic activity and cardioselectivity are listed in Table III.

Myocardial actions and hemodynamics—in vitro effects: Racemic sotalol and both the d and l isomers of sotalol cause similar increases in the action potential duration (APD) of cardiac tissue (for review, see Singh et al[31]). Associated with the increase in APD is an increase in cardiac contractility by racemic sotalol as well as its d and l-isomers. In 1968, Kaumann and Olson[32] first reported that sotalol caused concentration-dependent (2×10^{-6} to 6×10^{-4} M) increases in the contractility of isolated kitten papillary muscles. Similar positive inotropic effects have been reported for isolated adult canine trabecular and Purkinje fibers.[33] In contrast to 13 other β blockers, sotalol was reported to have no stimulant effect on left atria or spontaneous heart rate of right atria of guinea pigs or kittens.[34] The cardiac stimulant effect of sotalol was modest, increasing tension approximately 20 to 40% above control values. Unlike the positive inotropic effects of dichloroisoproterenol DCI, pronetholol, alprenolol and pindolol, those of sotalol were not reduced by reserpine pretreatment, or prior α- and β-receptor blockade by phenoxybenzamine and propranolol, respectively (Fig. 7).[34] Thus, the inotropic effect of sotalol is not due

P, 24, 176

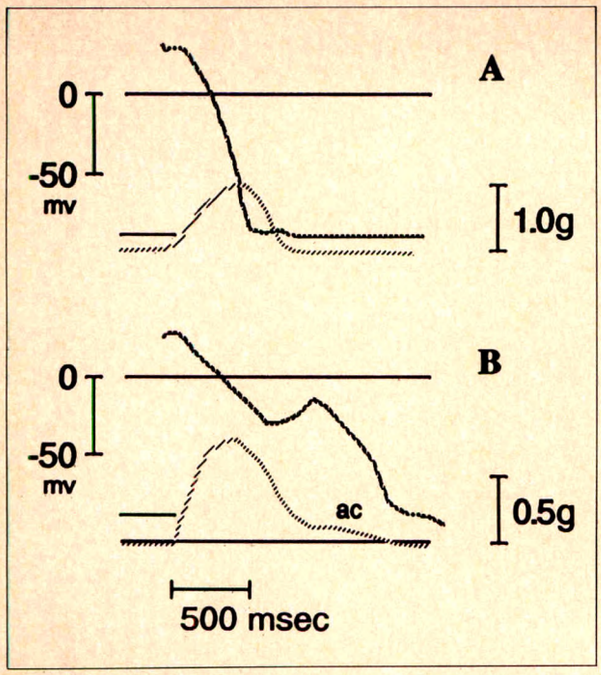


FIGURE 8. ***A*, control effects of sotalol (2×10^{-3} M) on feline papillary muscle. *B*, 97 minutes after washout. Note the oscillation: ac = aftercontraction. (Adapted from *Science*.[32])**

to intrinsic sympathometic activity of the drug but, rather, appears to be related to ionic changes that are also responsible for the increase in APD.[33] This has been variously attributed to an inhibition of the i_k or time-dependent K^+ current,[35] an increase in the magnitude of the slow inward Ca^{2+} current,[32,33] or an induction of Na^+-Ca^{2+} exchange.[33]

Like the increase in APD caused by sotalol, the positive inotropic effect is also inversely related to cardiac rate.[33,34]

An interesting feature of the positive inotropic effect of sotalol is aftercontraction (the late tonic component after partial relaxation from contraction). After high concentrations of sotalol (>10^{-4} M), the APD becomes markedly prolonged and, during the sustained plateau, the membrane potential begins to oscillate and is associated with an aftercontraction.[32,36] An example of the cardiac stimulant effects of sotalol in kitten papillary muscles as well as the aftercontraction at high concentrations is shown in Figure 8. The aftercontraction is related to Ca^{2+} because doubling the calcium concentration in the external solution increased the aftercontraction induced by sotalol over 300%.[32] Like both the APD prolongation and positive inotropic activities of sotalol, the magnitude of the aftercontraction appears to be inversely related to cardiac frequency.[33,34]

The membrane oscillation over the plateau range of the action potential induced by sotalol may have clinical relevance since it may be causally related to an unusual arrhythmia accompanying sotalol usage, namely torsades de pointes.[22] This arrhythmia is often associated with marked bradycardia, prolonged QT, hypokalemia and high doses of sotalol, and appears to be initiated by triggered activity.[22,37,38]

In vivo effects in experimental animals: Intracoronary injections of sotalol (17 to 4,400 μg) in anesthetized dogs had no effect on coronary flow, coronary vascular resistance, heart rate, contractile force or mean arterial

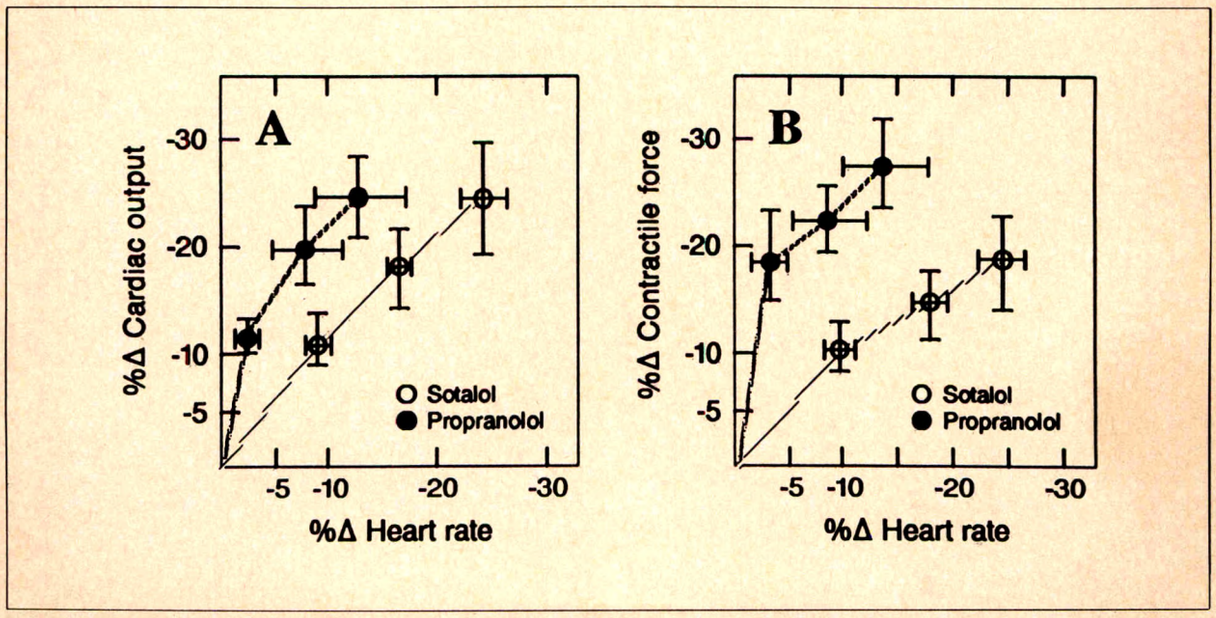


FIGURE 9. Percentage reductions in aortic flow (*A*) and contractile force (*B*) at the simultaneously recorded percent decreases in heart rate after each of 3 intravenous doses of sotalol (0.5, 2, and 8 mg/kg) or propranolol (0.0625, 0.25, and 1 mg/kg) in separate groups of 5 to 8 reserpine-treated atropinized dogs. Mean values ± standard error of the mean are indicated. (Adapted from *Arch Int Pharmacodyn Ther*.[29])

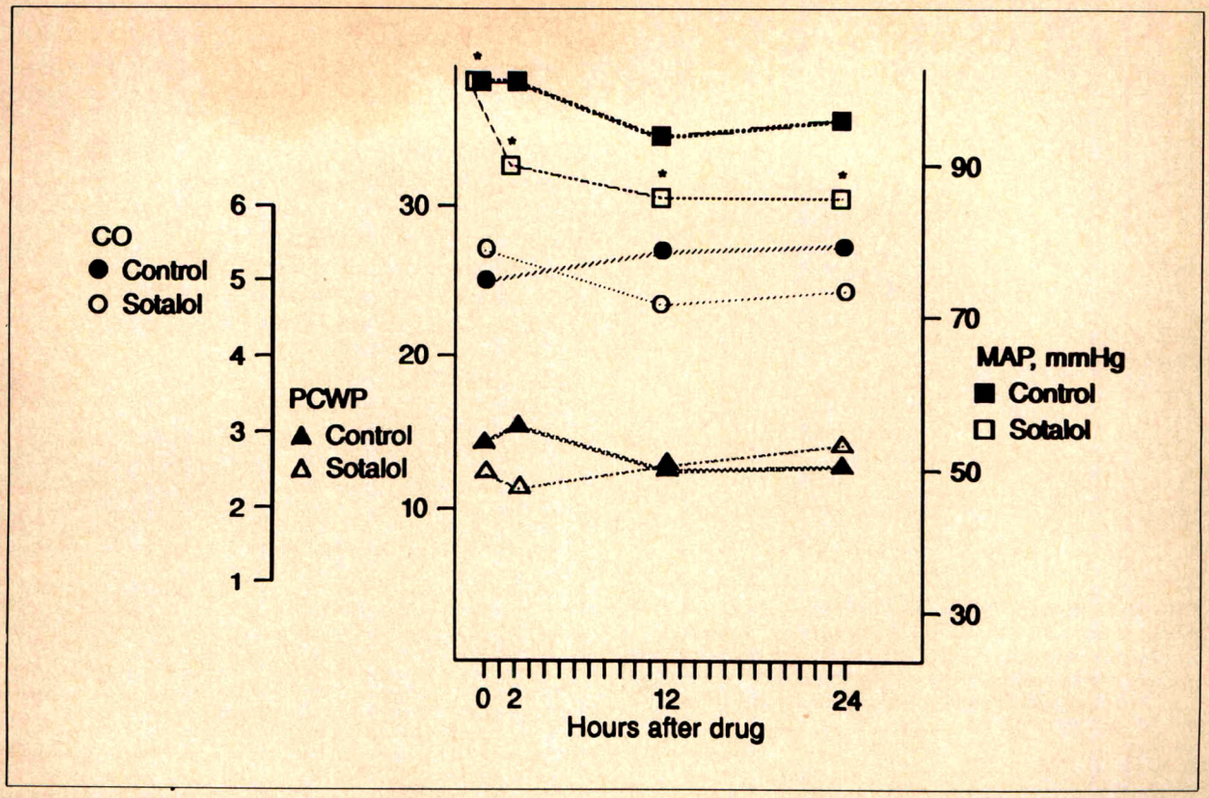


FIGURE 10. Hemodynamic changes in 30 patients with an acute myocardial infarction of less than 12 hours' duration after 40 to 120 mg of intravenous sotalol. CO = cardiac output; MAP = mean arterial blood pressure; PCWP = mean pulmonary capillary wedge pressure. (Adapted from *South Afr Med J.*[43])

perfusion pressure.[25] When infused at a constant rate of 0.31 mg/kg/min (as opposed to a bolus injection) to anesthetized dogs, sotalol had no effect on cardiac output, mean arterial blood pressure and total peripheral or pulmonary resistance, while actually increasing stroke volume despite a reduction in heart rate.[25] In anesthetized baboons, sotalol decreased cardiac output and heart rate, but stroke volume, left ventricular (LV) stroke work index and renal blood flow were unchanged.[39]

At equiactive β-blocking doses, in both the presence and absence of sympathetic tone (reserpine pretreatment and atropine), propranolol caused greater decreases in both right ventricular contractile force and LV dP/dt, and greater elevations in LV end-diastolic pressure than sotalol in an aortic bypass model in anesthetized dogs.[28] Furthermore, for any given decrease in heart rate, propranolol caused greater depression of myocardial contractility than did sotalol (Fig. 9).

Effects in patients with heart disease: The modest cardiac stimulant effects of sotalol in vitro and the relative lack of intrinsic negative inotropy in vivo in animals appear to be reflected in human hemodynamic studies. In patients with cardiac disease, sotalol administered at an i.v. dose of 0.2 mg/kg caused significant reductions in heart rate, systolic pressure, cardiac output and external cardiac work, whereas systolic pressure, pulmonary arterial pressure, stroke volume and systemic vascular resistance were unchanged.[40] In a second group of patients, sotalol decreased LV dP/dt_{max} with no change in LV end-diastolic pressure.[30]

Similar results in patients with cardiac disease were obtained by Thumala et al,[41] who found that 0.34 mg/kg of i.v. sotalol caused reductions, both at rest and during exercise, of heart rate, cardiac index, LV dP/dt and LV work. LV end-diastolic pressure was elevated while pulmonary resistance and pressure were unchanged. In patients with cardiac failure, i.v. doses of sotalol ranging from 0.2 to 0.6 mg/kg reduced heart rate and cardiac output with no change in stroke volume or LV end-diastolic volume.

In patients with acute myocardial infarction, i.v. sotalol (administered to a plasma level of 1.4 μg/ml) given within 24 hours of onset caused significant reductions in heart rate, systolic blood pressure and cardiac output with an additional, although transient, reduction in stroke volume. Both the systolic and diastolic pulmonary arterial pressures were slightly but significantly increased after administration of sotalol.[42]

Recently, Lloyd et al[43] examined the effects of i.v. sotalol (40 to 120 mg) in 28 patients with an acute myocardial infarction (mean of 6 hours after chest pain) and documented arrhythmias. Sotalol reduced heart rate and mean arterial pressure with no change in pulmonary capillary wedge pressure or systemic vascular resistance (Fig. 10). LV end-diastolic volume was unchanged in all but 4 patients with sotalol; in these 4, it was significantly

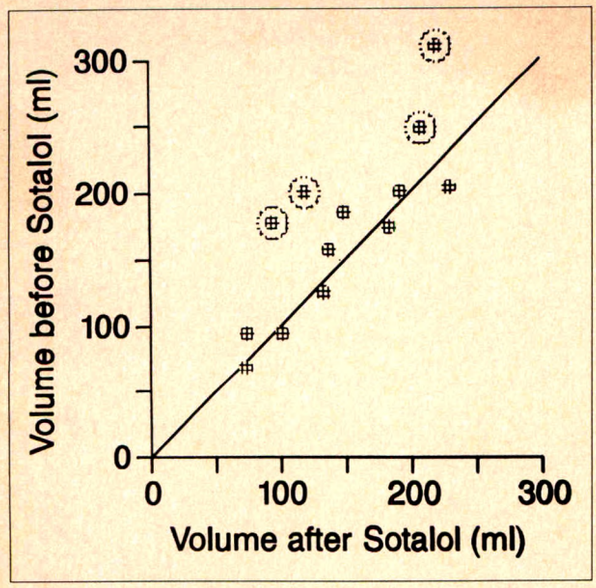


FIGURE 11. Radionuclide derived left ventricular end-diastolic volume before and after sotalol, 40 to 120 mg/kg administered intravenously as in Figure 10. *Large circles* indicate patients in whom left ventricular end-diastolic volume decreased after sotalol administration (Adapted from *South Afr Med J.*[43])

reduced (Fig. 11). Ejection fractions before sotalol was given (48.7 ± 15.5%) were not significantly altered by the drug (50.3 ± 16.4%); thus, stroke volume remained constant.

Thus, the hemodynamic effects of i.v. sotalol were consistent in patients with many types of heart disease, even with congestive heart failure or acute myocardial infarction. The effects are those expected with a β-adrenoceptor antagonist with little or no negative intrinsic inotropic activity and are characterized by a reduction in cardiac output largely mediated by a reduction in heart rate with stroke volume and other measures of LV function being largely preserved.

Results similar to those observed with i.v. sotalol have been observed with oral sotalol in patients with frequent and repetitive ventricular premature complexes (≥30/hour) and depressed cardiac function (mean ejection fraction 43 ± 15%). Sotalol (either 160 or 320 mg given twice daily) caused significant reductions in heart rate and systolic blood pressure at rest and during exercise, whereas cardiac index was unchanged.[44] LV ejection fraction, end-diastolic (but not systolic) volume index and stroke volume index actually increased in these patients. Thus, despite reductions in heart rate and increases in LV end-diastolic volume, sotalol did not adversely affect cardiac function because cardiac index and LV systolic volume did not change. Moreover, ejection fraction actually increased in patients whose arrhythmias were controlled and who had significant underlying heart disease.

Similar results were reported by Burckhardt et al[45] in patients with coronary artery disease and frequent complex arrhythmias. Oral sotalol (320 mg given 4 times daily) significantly reduced heart rate and systolic blood pressure both at rest and during exercise. However, the ejection fractions of patients receiving placebo or sotalol both at rest (43.8 ± 4.0% vs 44.6 ± 3.4%) and during exercise (41.3 ± 5.8% vs 44.8 ± 4.9%) were not different.

CONCLUSIONS

Sotalol has virtually ideal pharmacokinetics and a unique pharmacodynamic profile. Its β-antagonistic and unique class III electrophysiologic activity along with its favorable associated hemodynamic profile contribute to its desirability as a particularly useful agent for both ventricular and supraventricular arrhythmias.

REFERENCES

1. Schnelle K, Garrett ER. Pharmacokinetics of the beta-blocker sotalol in dogs. *J Pharm Sci 1973;62:362–375.*
2. Anttila M, Arstila M, Pfeffer M, Tikkanen R, Vallinkoski V, Sundquist H. Human pharmacokinetics of sotalol. *Acta Pharmacol Toxicol 1976;39:118–128.*
3. O'Hare MF, Leahey W, Murnaghan GA, McDevitt DG. Pharmacokinetics of sotalol during pregnancy. *Eur J Clin Pharmacol 1983;24:521–524.*
4. Bender W, Greil W, Ruther E, Schnelle K. Effects of the beta-adrenoceptor blocking agent sotalol on CNS: sleep, EEG, and psychophysiological parameters. *J Clin Pharmacol 1979;19:505–512.*
5. Sundquist H. Basic review and comparison of beta-blocker pharmacokinetics. *Curr Ther Res 1980;28:38S–44S.*
6. Blair AD, Burgess ED, Maxwell BM, Cutler RE. Sotalol kinetics in renal insufficiency. *Clin Pharmacol Ther 1981;29:457–463.*
7. Tjandramaga TB, Thomas J, Verbeeck R, Verbesselt R, Verberckmoes R, DeSchepper PJ. The effect of end-stage renal failure and haemodialysis on the elimination kinetics of sotalol. *Br J Clin Pharmacol 1976;3:259–265.*
8. Fourtillan JB, Lefebvre MA, Courtois Ph, Saux MC. Étude pharmacokinetique du sotalol chez l'homme sain par chromatographie liquide haute performance. *Therapie 1981;36:457–463.*
9. Poirier JM, Aubry JP, Cheymol G, Jaillon P. Pharmacokinetique du sotalol administre par voie veineuse chez le sujet sain. Application de la chromatographique liquid à haute performace. *Therapie 1981;36:465–471.*
10. Sotaniemi EA, Anttila M, Pelkonen RO, Jarvensivu P, Sundquist H. Plasma clearance of propranolol and sotalol and hepatic drug-metabolizing enzyme activity. *Clin Pharmacol Ther 1979;26:153–161.*
11. Sundquist HK, Anttila M, Forsstrom J, Kasanen A. Serum levels and half-life of sotalol in chronic renal failure. *Ann Clin Res 1975;7:442–446.*
12. Berglund G, Descamps R, Thomis JA. Pharmacokinetics of sotalol after chronic administration to patients with renal insufficiency. *Eur J Clin Pharmacol 1980;18:321–326.*
13. Ishizaki T, Hirayama H, Tawara K, Nakaya H, Sato M, Sato K. Pharmacokinetics and pharmacodynamics in young normal and elderly hypertensive subjects: a study using sotalol as a model drug. *J Pharmacol Exp Ther 1980;212:173–181.*
14. Sundquist H, Anttila M, Simon A, Reich JW. Comparative bioavailability and pharmacokinetics of sotalol administered alone and in combination with hydrochlorothiazide. *J Clin Pharmacol 1979;19:557–564.*
15. Sotaniemi EA, Anttila M, Rautio A, Stengard J, Saukko P, Jarvensivu P. Propranolol and sotalol metabolism after a drinking party. *Clin Pharmacolol Ther 1981;29:705–710.*
16. Kahela P, Anttila M, Tikkanen R, Sundquist H. Effect of food, food constituents and fluid volume on the bioavailability of sotalol. *Acta Pharmacol Toxicol 1979;44:7–12.*
17. Lish PM, Shelanski MV, LaBudde JA, Williams WR. Inhibition of cardiac chronotropic action of isoproterenol by sotalol (MJ 1999) in rat, dog and man. *Curr Ther Res 1967;9:311–324.*
18. Ishizaki T, Tawara K. Relationship between pharmacokinetics and pharmacodynamics of the beta adrenergic blocking drug sotalol in dogs. *J Pharmacol Exp Ther 1979;211:331–337.*
19. Gomoll AW, Bartek M. Comparative beta-blocking activities and electrophysiologic actions of racemic sotalol and its optical isomers in anesthetized dogs. *Eur J Pharmacol 1986;132:123–135.*
20. Brown HC, Carruthers SG, Kelly JG, McDevitt DG, Shanks RG. Observations on the efficacy and pharmacokinetics of sotalol after oral administration. *Eur J Clin Pharmacol 1976;9:367–372.*
21. Harron DWG, Balnave K, Kinney CD, Wilson R, Russell CJ, Shanks RG. Effects of exercise tachycardia during forty-eight hours of a series of doses of atenolol, sotalol and metoprolol. *Clin Pharmacol Ther 1981;29:295–302.*
22. Singh B. Historical development of the concept of controlling cardiac arrhythmias by lengthening repolarization: particular reference to sotalol. *Am J Cardiol 1990;65:suppl:3A–11A.*
23. Larsen AA, Lish PM. A new bio-isostere: alkylsulphonamidophenethanolamines. *Nature (Lond) 1964;203:1283–1284.*
24. Lish PM, Weikel JH, Dungan KW. Pharmacological and toxicological prop-

erties of two new beta-adrenergic receptor antagonists. *J Pharmacol Exp Ther 1965;149:161–173.*
25. Stanton HC, Kirchgessner T, Parmenter K. Cardiovascular pharmacology of two new beta-adrenergic receptor antagonists. *J Pharmacol Exp Ther 1965;149: 174–182.*
26. Blinks JR. Evaluation of the cardiac effects of several beta-adrenergic blocking agents. *Ann NY Acad Sci 1967;139:673–685.*
27. Manley BS, Alexopoulos D, Robinson GJ, Cobbe SM. Subsidiary class III effects of beta-blockers? A comparison of atenolol, metoprolol, nadolol, oxprenolol and sotalol. *Cardiovas Res 1986;20:705–709.*
28. Gomoll AW, McKinney GR. Sotalol: cardiac and haemodynamic actions in the anesthetized dog. In: Snart A, ed. Advances in Beta-Adrenergic Blocking Therapy—Sotalol, vol. 1. Amsterdam: *Excerpta Medica, 1974:6–72.*
29. Gomoll AW, Braunwald E. Comparative effects of sotalol and propranolol on myocardial contractility. *Arch Int Pharmacodyn Ther 1973;205:338–354.*
30. Gomoll AW, Barek MJ. Comparative beta-blocking activities and electrophysiologic actions of racemic sotalol and its optical isomers in anesthetized dogs. *Eur Pharmacol 1986;132:123–135.*
31. Singh BN, Deedwania P, Nademanee K, Ward A, Sorkin EM. Sotalol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use. *Drugs 1987;34:311–349.*
32. Kaumann AJ, Olson CB. Temporal relation between long-lasting aftercontractions and action potentials in cat papillary muscles. *Science 1968;161:293–295.*
33. Lanthrop DA. Electromechanical characterization of the effects of racemic sotalol and its optical isomers on isolated canine ventricular trabecular muscles and Purkinje strands. *Can J Physiol Pharmacol 1985;63:1506–1512.*
34. Kaumann A, Blinks JR. Stimulant and depressant effects of beta-adrenoceptor blocking agents on isolated heart muscle. *Naunyn Schmiedebergs Arch Pharmacol 1980;311:205–218.*
35. Carmeliet E. Electrophysiologic and voltage clamp analysis of the effects of sotalol on isolated cardiac muscle and Purkinje fibers. *J Pharmacol Exp Ther 1984;232:817–825.*
36. Lewis MJ, Grey AC, Henderson AH. Inotropic beta-blocking potency (pA_2) and partial agonist activity of propranolol, practolol, sotalol and acebutolol. *Eur J Pharmacol 1983;86:71–76.*
37. Krikler DM, Curry PVL. Torsade de pointes, an atypical ventricular tachycardia. *Br Heart J 1976;38:117–120.*
38. Laakso M, Aberg A, Savola J, Pentikainen PJ, Pyrorala K. Diseases and drugs causing prolongation of the QT interval. *Am J Cardiol 1987;59:862–865.*
39. Rogers GG, Rosendorff C, Shimell CJ, Coull A, Bomzon L. Effect of peroral administration of sotalol on the hemodynamics of the baboon. *J Cardiovasc Pharmacol 1982;4:197–204.*
40. Hutton I, Lorimer AR, Hillis WS, McCall D, Reid JM, Lawrie TDV. Haemodynamics and myocardial function after sotalol. *Br Heart J 1972;34:787–790.*
41. Thumala A, Hammermeister KE, Campbell WB, Pomerantz B, Overy H, Davies H. Hemodynamic studies with sotalol in man, performed at rest, during exercise, and during right ventricular pacing. *Am Heart J 1971;82:439–447.*
42. Astrom M, Edhag O, Nyquist O, Vallin H. Haemodynamic effects of intravenous sotalol in acute myocardial infarction. *Eur Heart J 1986;7:931–936.*
43. Lloyd EA, Charles RG, Gordon GD, Adams CM, Mabin TA, Commerford PJ, Opie LH. Beta-blockade by sotalol in early myocardial infarction decreases ventricular arrhythmias without increasing left ventricular volume. *South Afr Med J 1988;74:5–10.*
44. Mahmarian JJ, Verani MS, Hohmann T, Hill R, Thornton BC, Bolli R, Young JB, Roberts R, Pratt CM. The hemodynamic effects of sotalol and quinidine: analysis by use of rest and exercise gated radionuclide angiography. *Circulation 1987;76:324–331.*
45. Burckhardt D, Pfisterer M, Hoffmann A, Burkart F, Emmenegger H, Jost M, Bolli P, Buehler F. Effects of the beta-adrenoceptor-blocking agent sotalol on ventricular arrhythmias in patients with chronic ischemic heart disease. *Cardiology 1983;70:114–121.*

Concentration/Response Relations for the Multiple Antiarrhythmic Actions of Sotalol

Raymond L. Woosley, MD, PhD, Jean T. Barbey, MD, Ted Wang, MD, and Christian Funck-Brentano, MD

Sotalol, one of the first β-receptor antagonists synthesized, is a promising investigational agent with remarkable efficacy for treatment of patients with ventricular and supraventricular arrhythmias. Unlike other β blockers, sotalol also possesses class III antiarrhythmic action, evidenced by prolongation of the myocardial action potential duration. This additional action probably accounts for the greater antiarrhythmic efficacy of sotalol compared with other β blockers.

Sotalol's class III antiarrhythmic action becomes apparent at concentrations higher than those necessary for significant β-receptor antagonism, both in vitro and in human subjects. In a study correlating dosage and antiarrhythmic response with prolongation of rate-corrected QT (QTc) (a measure of class III action) and the degree of β-receptor blockade (assessed by the reduction of the maximal exercise-induced heart rate), 11 of 17 patients had an antiarrhythmic response. Eight of these 11 responders had been unresponsive to conventional β-receptor antagonists. The plasma concentration associated with significant QTc prolongation (2.55 μg/ml) was found to be much greater than that associated with 50% reduction in maximal slowing of heart rate (0.8 μg/ml). As with other β-receptor antagonists, the activities of sotalol's 2 stereoisomers differ, with the l-isomer having far more β-blocking activity. However, both isomers have equal class III antiarrhythmic activity. When increasing doses of the d-isomer of sotalol (50 to 400 mg every 12 hours) were evaluated in patients with chronic ventricular arrhythmias, arrhythmia frequency was suppressed >80% in 3 patients and 50% in 1 patient. With 800 mg/day, QTc was prolonged by 12.3 ± 7% ($p < 0.01$) and the decrease in heart rate at rest by 19.3 ± 8.4% ($p < 0.05$) and during peak exercise by 12.3 ± 7% ($p < 0.001$) compared with placebo. One interpretation of the observed slowing of the heart rate could be that d-sotalol has clinically significant β-receptor antagonist properties. However, a comparison of the effects of d-sotalol with those of atenolol (a β-blocker without class III activity) on indicators of β-receptor antagonism showed that d-sotalol slows heart rate predominantly by prolonging repolarization. d-Sotalol reduces heart rate predominantly at short cycle lengths, when action potential duration has its maximal contribution to heart rate. Furthermore, the degree of reduction in exercise heart rate with d-sotalol correlated with the increase in QT interval, and d-sotalol did not alter blood pressure. Therefore, the conclusion of these studies is that d-sotalol is an effective antiarrhythmic agent due predominantly to its class III action. Racemic sotalol has predominantly β-blocking activity at low dosages and has increasing degrees of class III antiarrhythmic action at higher dosages.

(Am J Cardiol 1990;65:22A–27A)

Sotalol is an investigational nonselective β-receptor antagonist lacking in intrinsic sympathomimetic activity or membrane-stabilizing effects. It is effective in the treatment of supraventricular tachycardia,[1–5] in the suppression of ventricular premature complexes (VPCs) and nonsustained ventricular tachycardia,[2–4,6,7] and in the treatment of inducible sustained ventricular tachycardia.[8–10] Sotalol's electrophysiologic actions were seen to differ significantly from those of other β-receptor blocking agents,[11] and subsequent investigations comparing sotalol's degree of antiarrhythmic efficacy to that of propranolol revealed that this difference held true for this parameter as well.[11]

Sotalol's pharmacologic properties have been described; however, their clinical significance and the range of concentrations over which these properties are displayed vary considerably. The atrial, but not the ventricular, effective refractory period is increased with low intravenous doses of sotalol (0.4 mg/kg),[12] whereas higher doses increase both the atrial and ventricular effective refractory period,[6,13] the monophasic action potential duration, and QTc.[14,15] In vitro data show that concentrations associated with significant slowing of the sinoatrial node conduction in rabbit atrial tissues are lower than those at which action potential and effective refractory period prolongation are observed in canine Purkinje fi-

From the Departments of Pharmacology and Medicine, and Division of Clinical Pharmacology, Georgetown University School of Medicine, Washington, D.C.; Departments of Medicine and Pharmacology, Tulane University Medical School, New Orleans, Louisiana; and Unité de Pharmacologie Clinique, Hôpital Saint-Antoine, Paris, France.

Address for reprints: Raymond L. Woosley, MD, PhD, Department of Pharmacology (NE 403), Georgetown University School of Medicine, 3900 Reservoir Road, N.W., Washington, D.C. 20007.

TABLE I Patient Characteristics

	No. of Pts.
Prior lack of response to β-receptor antagonists	
Propranolol (240 to 320 mg/day)	5
Timolol (40 to 80 mg/day)	5
Atenolol	1
Metoprolol	1
Prior response to β-receptor antagonists	
Timolol (20 mg/day)	1

Reprinted with permission from *Am J Cardiol.*[6]

bers (10^{-4} vs 10^{-3} M, respectively),[13] suggesting that these effects might be dissociable. In our studies of patients receiving sotalol therapy, substantial β blockade is evident at plasma concentrations generally lower than those associated with QTc prolongation.

Sotalol's electrophysiologic effects do differ from those associated with β-receptor blockade, in that they occur predominantly at concentrations higher than those producing β-receptor antagonism.[1,16,17] Both in vivo and in vitro studies have revealed that sotalol increases the action potential duration and effective refractory period without changing conduction velocity or the slope of the phase 0 upstroke of the cardiac action potential.[13,14,16,18] The increased refractoriness is thought to be due to time-dependent block of the outward potassium current.[19]

A study of patients with nonsustained ventricular arrhythmias[20] showed an increase in the proportion of patients successfully treated with sotalol as the dosage was increased from 160 to 640 mg/day. However, no data on plasma concentration, β blockade or change in QTc were reported for this group.

CONCENTRATION-DEPENDENT PHARMACOLOGIC PROPERTIES OF SOTALOL

The concentration dependence of sotalol's β-receptor and class III antiarrhythmic effects was reported[1] in a population of patients with chronic high-frequency, asymptomatic, ventricular arrhythmias (Table I). Twelve of these 17 patients had previously demonstrated a lack of response to therapy with β-receptor antagonists (Table I). Current antiarrhythmic medication was withheld for at least 4 elimination half-lives, and arrhythmia frequency was then assessed using continuous telemetric electrocardiographic monitoring and recording during an initial 2-day, baseline placebo period. Laboratory tests and 2 treadmill tests (1 for training) using the standard Bruce protocol were also performed. Patients having at least 1 VPC per minute during the drug-free baseline period were entered into a dose-ranging stage. Initially, sotalol was administered once daily; however, due to the development of torsades de pointes in 1 of the first 7 patients, the regimen was changed to divided dosages given twice daily (10 patients). Patients received 160 mg/day of sotalol for the first 3 days. Steady-state equilibrium was assumed to have been reached on the third day, and immediately preceding the morning dose on this day, a 12-lead resting electrocardiogram (ECG), 24-hour am-

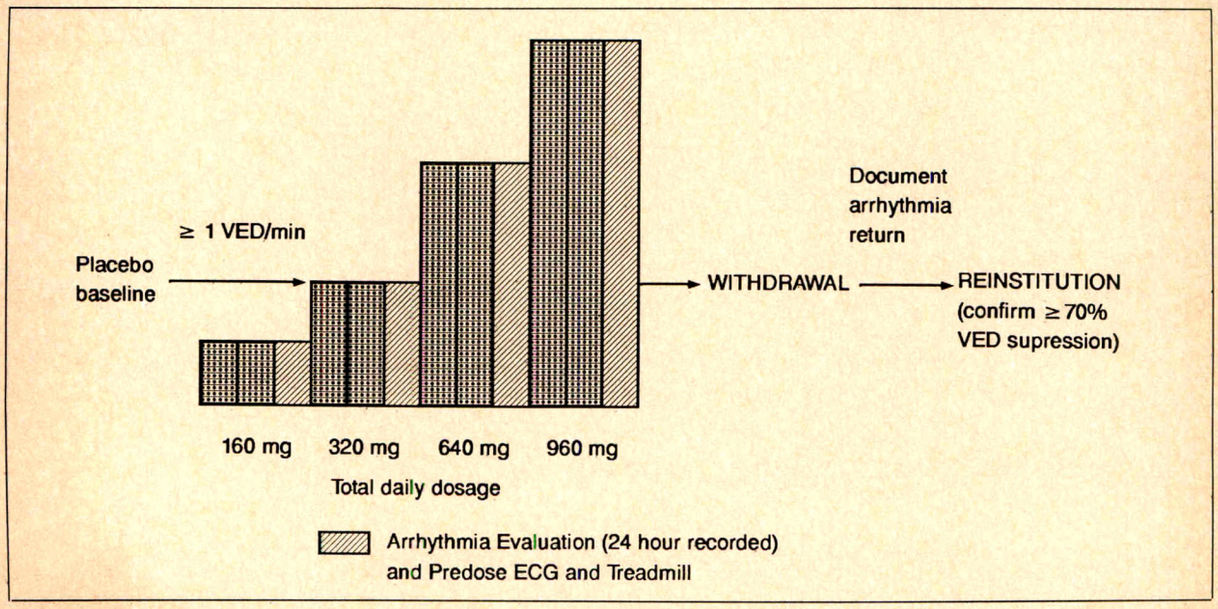


FIGURE 1. Protocol for evaluation of dosage, β-adrenergic receptor blocking activity, and antiarrhythmic response during a study of the effects of sotalol in patients with chronic, high-frequency ventricular premature complexes. On the third day at a given sotalol dosage (when steady-state equilibrium was assumed to have been achieved), a treadmill exercise test, electrocardiography (ECG) and 24-hour recorded arrhythmia evaluation were performed. Once a dosage was found to produce >70% suppression of the arrhythmia, placebo was substituted for active drug. Placebo therapy was maintained until arrhythmia frequency returned to at least 50% of baseline, at which time the previously effective dosage of sotalol was reinstituted to confirm antiarrhythmic response. VED = ventricular ectopic depolarization. (Reprinted with permission from *Am J Cardiol.*[6])

TABLE II Antiarrhythmic Response to Sotalol

	No. of Pts.
Confirmed response	11
Response not confirmed	1
No response to maximal dosage	2
Excluded from study (highly variable baseline VPCs)	1
Withdrew due to adverse effects	
Torsades de pointes (640 mg/day)	1
Gastrointestinal symptoms (640 mg/day)	1

VPCs = ventricular premature complexes.
Reprinted with permission from *Am J Cardiol.*[6]

bulatory ECG recording, exercise treadmill test and blood sample for measurement of trough plasma sotalol concentration were obtained. Arrhythmia suppression was defined as 70% or greater VPC reduction in 24-hour arrhythmia frequency compared with baseline. In the absence of arrhythmia suppression or limiting adverse effects, dosage was sequentially increased to 320, 640 or 960 mg/day, again given for 3 days (Fig. 1).

Sotalol was discontinued if arrhythmia suppression was achieved with less than the maximal dosage, or when the maximal dosage (960 mg/day) was reached. On the morning of the last dose, blood samples were obtained before dosage and again at 15 times over the subsequent 72 hours. Placebo was substituted for sotalol, and arrhythmia quantitated either for 3 days or until arrhythmia frequency returned to >50% of baseline, whichever was longer. For those patients who had demonstrated 70 to 100% suppression of VPCs, the apparently effective sotalol dose was reinstituted for 3 days.

Reduction in the maximal exercise-induced heart rate was used as an index of β-blockade, with the data being fitted to the Hill equation: $R = (R_{max})(C)/(C_{50} + C)$ where C is measured plasma sotalol concentration, R is observed percent reduction of the maximal exercise heart rate, R_{max} is maximal reduction in heart rate expressed as a percentage (fitted), and C_{50} is sotalol concentration at which 50% of R_{max} occurred (fitted). Given the observed C and R values, a computer program (SAAM 27) was used to determine the most appropriate values for R_{max} and C_{50}. Measurement of arrhythmia frequency, sotalol plasma concentration, and determination of sotalol elimination half-life and oral clearance are described by Wang et al.[6]

Unlike the case of agents having complex pharmacokinetics and active metabolites, the route of sotalol administration has little affect on the effects observed. For each patient in this study, the trough plasma concentration of sotalol increased linearly as the oral dosage was

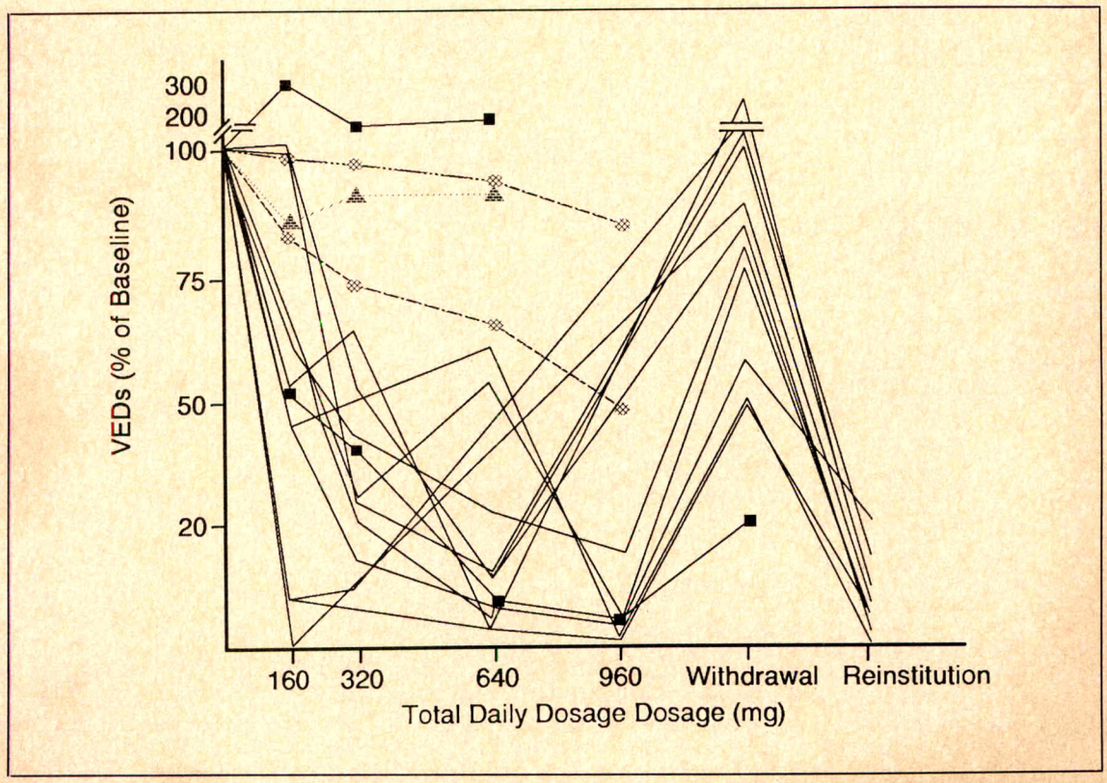


FIGURE 2. Relation between sotalol dosage and arrhythmia frequency in 16 patients with chronic high-frequency ventricular premature complexes. Data for the 11 patients having a confirmed antiarrhythmic response to sotalol are shown by *solid lines*. One patient's response was not confirmed (*squares*), 2 patients failed to respond even at the maximal dosage (*circles*), and 2 patients experienced adverse reactions (torsade de pointes [*triangles*] and gastrointestinal side effects [*squares*]). (Reprinted with permission from *Am J Cardiol.*[6])

increased. After termination of sotalol dosage, plasma concentrations decreased exponentially, with the elimination half-life ranging from 9.5 to 28.3 hours (mean of 15.9 ± 1.5). The elimination half-life was 20 hours or longer in 4 patients. Sotalol's oral clearance ranged from 118 to 386 ml/min (mean 192 ± 19).

Eleven of the 17 patients had a reproducible antiarrhythmic response to sotalol (Table II) and 4 of these continued to receive therapy 2 and 3 years later. In the remaining 6 patients, sotalol was discontinued because of adverse effects (dyspnea, bradycardia, and psychosis [3, 1 and 1 patient, respectively]), or recurrence of arrhythmia (2 patients, 1 each at 7 and 20 months). The effect of increasing sotalol dosage on VPC frequency is shown in Figure 2.

The relation between sotalol plasma concentration and VPC suppression, QTc lengthening and reduction in exercise heart rate is shown in Figures 3 and 4. The concentration predicted to produce 50% reduction in maximal heart rate (C_{50}) was 804 ng/ml (at an estimated oral dosage of 282 mg/day), a value considerably lower than the concentration associated with significant increases in QTc (2,550 ng/ml reached at a mean oral dosage of 969 mg/day). Suppression of VPCs occurred at low sotalol concentration (less than 1,000 ng/ml) in 6 of 11 patients responding and at 1,300 to 3,400 ng/ml in the other 5 responders (Fig. 5). Three of the patients who had previously failed to respond to other β-receptor antagonists (and the 1 patient who had responded to timolol) responded to low concentrations of sotalol. Thus, when dosage was correlated with action potential duration and the degree of β-receptor blockade, not only did a significant number of patients demonstrate an antiarrhythmic response, but also plasma sotalol concentrations associated with the 2 effects were found to be different.

EFFECTS OF d-SOTALOL

The dextroisomer of sotalol (d-sotalol) possesses the repolarization-prolonging effects of racemic sotalol while having only minimal β-blocking properties. Its efficacy and safety were tested in 8 patients with chronic ventricular arrhythmias who had not responded to several (5 ± 3.9) other antiarrhythmic drugs, and who had also failed to respond to trials of several β-receptor blocking agents.

After a placebo period, each patient received increasing doses of d-sotalol (50 to 400 mg every 12 hours) for 3-

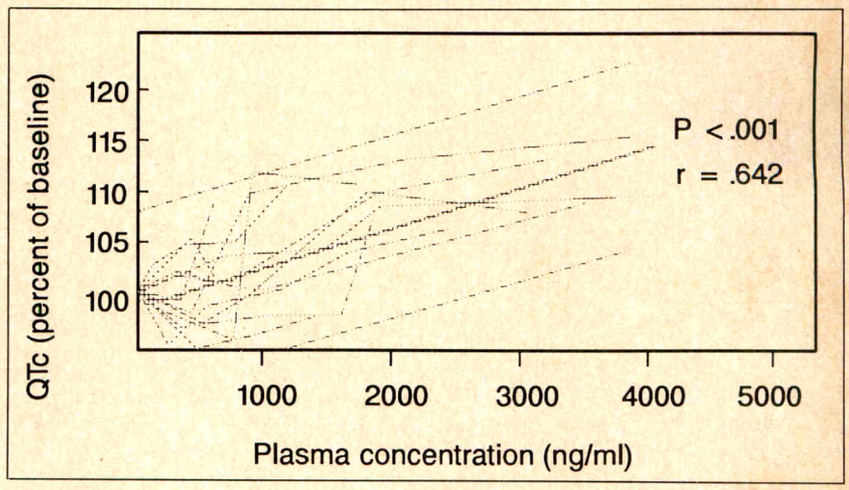


FIGURE 3. Relation between sotalol plasma concentration and cardiac electrophysiologic response–measured prolongation of QTc over baseline. The lower 95% confidence limit rises above baseline at a sotalol concentration of 2,550 ng/ml. (Reprinted with permission from *Am J Cardiol.*[6])

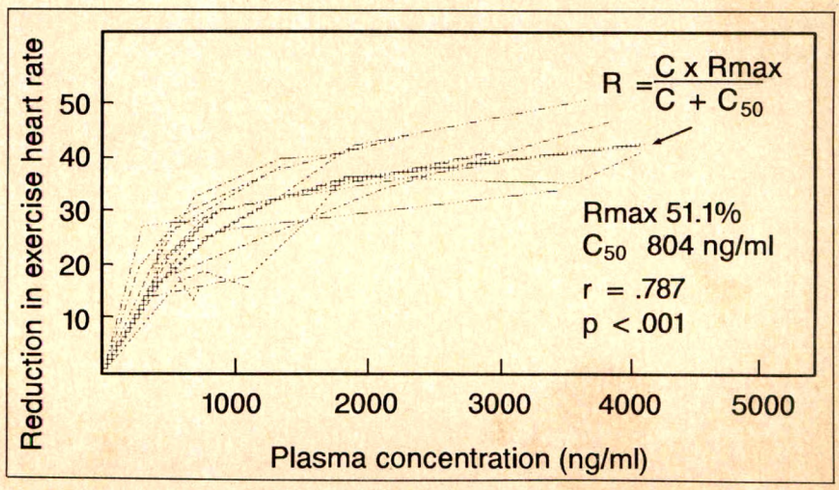


FIGURE 4. Beta-adrenergic receptor blockade, measured as percent reduction (R) in exercise heart rate, as a function of plasma sotalol concentration. R_{max} = maximal modeled reduction, C_{50} = concentration (C) producing 50% of R_{max}. (Reprinted with permission from *Am J Cardiol.*[6])

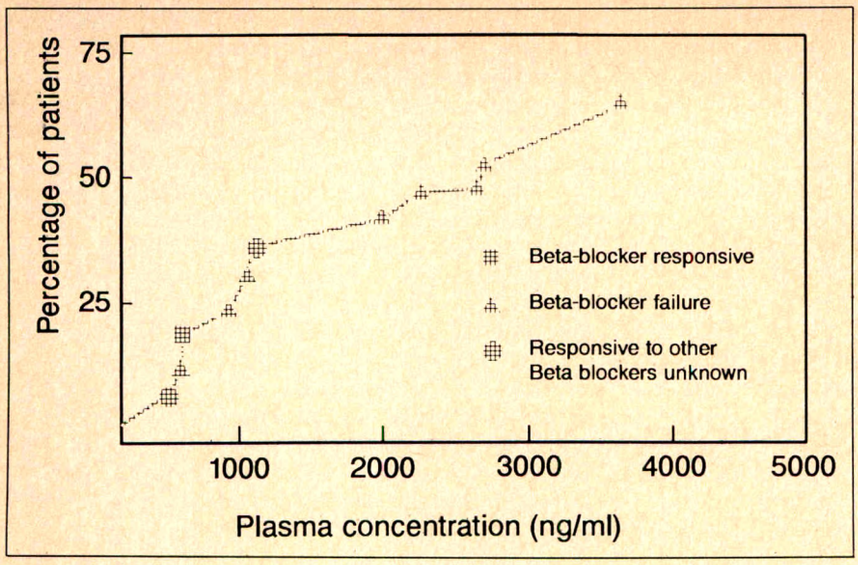


FIGURE 5. Relation between plasma sotalol concentration and the percentage of patients demonstrating >70% arrhythmia suppression during 24-hour Holter monitoring. Eight of these patients had previously failed to respond to other β-adrenergic receptor inhibitors (*triangles*), 1 had responded to timolol (*squares*) and 2 had not been evaluated (*circles*). See Table I for details of previous dosage. (Reprinted with permission from *Am J Cardiol.*[6])

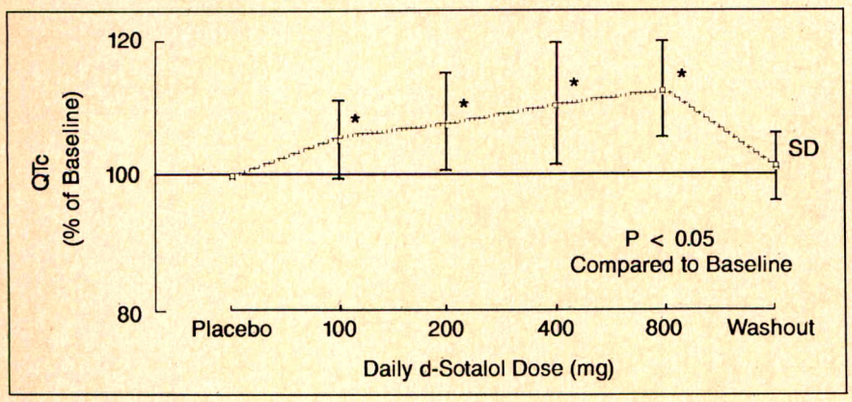


FIGURE 6. QTc prolongation as a function of daily d-sotalol dosage. d-Sotalol was administered orally to 8 patients with chronic ventricular arrhythmias. After a placebo period, each patient received increasing doses of d-sotalol (50 to 400 mg every 12 hours) for 3-day periods. See the text for further details. SD = standard deviation.

day periods. Ventricular arrhythmias were suppressed by >80% in 3 of the 8 patients given dosage regimens of 200 mg every 12 hours (n = 2) or 400 mg every 12 hours (n = 1). Ventricular arrhythmias were suppressed 50% in 1 patient receiving 200 mg every 12 hours. Increasing d-sotalol from 200 mg every 12 hours to double that amount every 12 hours caused fatigue and malaise in more than one-half of the patients (4 of 7) but substantially improved arrhythmia suppression in only 1 patient. When compared with placebo, changes in electrophysiologic parameters measured at a dosage of 800 mg/day of d-sotalol were 13 ± 9% prolongation of QTc ($p < 0.01$). The relation between sotalol dosage and QTc prolongation is shown in Figure 6. These results prove antiarrhythmic activity for the d-isomer of sotalol in humans.[21] However, the reduction in heart rate raised the possibility that d-sotalol may have significant β-receptor blocking properties. Whether this was because of contamination by l-sotalol or inherent pharmacologic properties was unclear.

TABLE III Comparison of Effects of d-Sotalol and Atenolol

	d-Sotalol	Atenolol	Placebo
Resting HR (beats/min)	54.4 ± 7.5*	47.7 ± 5.5†	58.4 ± 6.8
CD_{25} (μg)	2.3 ± 1.3†	1.8 ± 1.1†	1.0 ± 0.5
Standing HR (beats/min)	71.9 ± 13*†	57.0 ± 7.6†	85.4 ± 9.3
Peak HR (beats/min)	164.7 ± 11*†	150.2 ± 10†	178.4 ± 8.2
Peak systolic (mm Hg)	159.0 ± 24*	147.5 ± 10†	163.7 ± 23
QTc (ms)	449.5 ± 32*†	397.9 ± 19	400.3 ± 31

* $p < 0.05$ vs atenolol.
† $p < 0.05$ vs placebo.
BP = blood pressure (mm Hg); CD_{25} = dose of isoproterenol raising heart rate 25 beats/min; HR = heart rate.
Adapted from *Clin Res.*[22]

A recent study[22,23] revealed that the mechanism of the decrease in heart rate produced by d-sotalol is predominantly due to prolongation of repolarization, correlating with prolongation of the QT interval. This was determined in a double-blind, randomized study performed on healthy subjects that compared the effects of d-sotalol with those of another β-adrenergic antagonist, atenolol, and placebo. Using treadmill exercise and isoproterenol tests, d-sotalol was found to produce a significant reduction in heart rate only at short cycle lengths when the action potential duration in the sinoatrial node would

have its maximal contribution to heart rate. This was in contrast to the effects of atenolol, which reduced heart rate at all cycle lengths (Table III). The reduction in exercise heart rate with d-sotalol correlated with the increase in QT interval ($p < 0.05$, $r = 0.75$), and, unlike atenolol, d-sotalol did not reduce blood pressure, an action seen during effective β blockade.

CONCLUSION

Sotalol is a unique β-receptor blocking agent that may prove especially beneficial for patients because of its dual pharmacologic actions. Whereas d-sotalol appears to be an effective antiarrhythmic agent predominantly because of its class III action, racemic sotalol produces β-adrenergic receptor blockade at lower dosages and displays increasing degrees of class III antiarrhythmic action at higher dosages. Because of its additional actions, sotalol possesses greater antiarrhythmic efficacy than is found with the other β-receptor antagonists.

Acknowledgment: We thank Rosemary Hoffman for providing editorial assistance.

REFERENCES

1. Rizos I, Segnes J, Jauernig R, Lengfelder W, Czygan E, Brachmann J, Kubler, W. Differential effects of sotalol and metoprolol on induction of paroxysmal supraventricular tachycardia. *Am J Cardiol 1984;53:1022–1027.*

2. Simon A, Berman E. Long-term sotalol therapy in patients with arrhythmias. *J Clin Pharmacol 1979;19:547–556.*

3. Fogelman F, Lightman SL, Sillett RW, McNicol MW. The treatment of cardiac arrhythmias with sotalol. *Eur J Clin Pharmacol 1972;5:72–76.*

4. Prakash R, Parmley WW, Allen HN, Matloff JM. Effect of sotalol in clinical arrhythmias. *Am J Cardiol 1972;29:397–400.*

5. Nathan AW, Hellestrand KJ, Bexton RS, Ward DE, Spurrell RAJ, Camm AJ. Electrophysiologic effects of sotalol—just another beta blocker. *Br Heart J 1982;47:515–520.*

6. Wang T, Bergstrand RH, Thompson KA, Siddoway LA, Duff HJ, Woosley RL, Roden DM. Concentration-dependent pharmacologic properties of sotalol. *Am J Cardiol 1986;57:1160–1165.*

7. Anderson JL, Askins JC, Gilbert EM, Miller RH, Keefe DL, Somberg JC, Freedman RA, Haft LR, Mason JW, Lessem JN. Multicenter trial of sotalol for suppression of frequent, complex ventricular arrhythmias: a double-blind, randomized, placebo-controlled evaluation of two doses. *JACC 1986;8:752–762.*

8. Nademanee K, Feld G, Hendrickson J, Singh PN, Singh BN. Electrophysiologic and antiarrhythmic effects of sotalol in patients with life-threatening ventricular tachyarrhythmias. *Circulation 1985;72:555–564.*

9. Senges J, Lengfelder W, Jauernig R, Czygan E, Brachmann J, Rizos I, Cobbe W, Kubler W. Electrophysiologic testing in assessment of therapy with sotalol for sustained ventricular tachycardia. *Circulation 1984;69:577–584.*

10. Steinbeck G, Bach P, Harberl R. Electrophysiologic and antiarrhythmic efficacy of sotalol for sustained ventricular tachyarrhythmias: evaluation by programmed stimulation and ambulatory electrocardiogram. *JACC 1986;8:949–958.*

11. Duff HJ, Wyse DG, Bond R, Hillier K, Mitchell LB. Sotalol-propranolol comparison. Relationships amongst antiarrhythmic efficacy, class III electrophysiologic action and beta blockade (abstr). *JACC 1984;3:558.*

12. Ward DE, Camm AJ, Spurrell RAJ. The acute cardiac electrophysiological effects of intravenous sotalol hydrochloride. *Clin Cardiol 1979;2:185–191.*

13. Edvardsson N, Hirsch I, Emanuelsson H, Ponten J, Olsson SB. Sotalol induced delayed ventricular repolarization in man. *Eur Heart J 1980;1:335–343.*

14. Echt DS, Berte LE, Clusin WT, Samuelsson RG, Harrison DC, Mason JW. Prolongation of the human cardiac monophasic action potential by sotalol. *Am J Cardiol 1982;50:1082–1086.*

15. Neuvonen PJ, Elonen E, Tanskanen A, Tuomilehto J. Sotalol prolongation of the QT_c interval in hypertensive patients. *Clin Pharmacol Ther 1982;32:25–32.*

16. Strauss HC, Bigger JT, Hoffman BF. Electrophysiological and beta-receptor blocking effects of MJ 1999 on dog and rabbit cardiac tissue. *Circ Res 1970;26:661–677.*

17. Kopelman HA, Woosley RL, Lee JT, Roden DM, Echt DS. Electrophysiologic effects of intravenous and oral sotalol for sustained ventricular tachycardia secondary to coronary heart diseases. *Am J Cardiol 1988;61:1006–1011.*

18. Singh BN, Vaughan Williams EM. A third class of antiarrhythmic action. Effects on atrial and ventricular intracellular potentials, and other pharmacological actions on cardiac muscle, of MJ 1999 and AH 3474. *Br J Pharmacol 1970;39:675–687.*

19. Carmeliet E. Electrophysiologic and voltage clamp analysis of effects of sotalol on isolated cardiac muscle and Purkinje fibers. *J Pharmacol Exp Ther 1985;232:817–825.*

20. Lidell C, Rehnqvist N, Sjorgren A, Yli-Uotila RJ, Ronnevik PK. Comparative efficacy of oral sotalol and procainamide in patients with chronic ventricular arrhythmias: A multicenter study. *Am Heart J 1985;109:970–975.*

21. Barbey JT, Echt DS, Thompson KA, Roden DM, Woosley RL. Effect of d-sotalol on ventricular arrhythmias in man (abstr). *Circulation 1985;72:suppl III:III-170.*

22. Funck-Brentano C, Roden DM, Woosley RL. Mechanism of the decreased heart rate by d-sotalol (abstr). *Clin Res 1988;36:363A.*

23. Funck-Brentano C, Roden DM, Woosley RL. A pragmatic approach to the calculation of the rate-corrected QT interval. *Eur Heart J; in press.*

Hemodynamic Effects of Intravenous and Oral Sotalol

John J. Mahmarian, MD, Mario S. Verani, MD, and Craig M. Pratt, MD

Beta-adrenergic blocking agents may have negative inotropic effects that are particularly worrisome in patients with depressed cardiac function. Their membrane-stabilizing properties may be a contributing factor. Sotalol is currently thought not to cause significant myocardial depression. Intravenous sotalol administration has minimal effects on resting stroke volume, although heart rate and consequently cardiac output are significantly decreased. Systolic blood pressure decreases, with a minimal change in diastolic or mean pressure. Hemodynamic effects are usually seen within 15 to 20 minutes of administration.

Hemodynamic indexes are maintained even in patients with mildly depressed ejection fractions (mean ejection fraction of 43 ± 15%) after oral sotalol administration. Although heart rate decreases, cardiac index is unchanged because of a significant increase in stroke volume index. The latter results from an increase in preload (secondary to bradycardia) and a decrease in afterload. Sotalol is well tolerated, although occasionally it may cause worsening heart failure. This is seen in patients with markedly depressed left ventricular function and inadequate cardiac reserve characterized by an inability to increase stroke volume and cardiac output with exercise. Long-term (1-year) patient follow-up reveals no significant hemodynamic deterioration from initial values obtained after oral administration.

(Am J Cardiol 1990;65:28A–34A)

From the Section of Cardiology, Baylor College of Medicine, Houston, Texas. Computational assistance was provided by the CLINFO project funded by grant RR-00350, Division of Research Resources, National Institutes of Health, Bethesda, Maryland.

Address for reprints: Craig M. Pratt, MD, The Methodist Hospital, Baylor College of Medicine, 6535 Fannin MS F1001, Houston, Texas 77030.

This report reviews the hemodynamic effects of sotalol as reported in both animal and human studies. Sotalol is a unique β blocker that lacks the membrane-stabilizing properties of more traditional nonselective β blockers, although it possesses class III antiarrhythmic effects. Beta blockers are generally regarded as negative inotropic agents and must be used cautiously in patients with depressed left ventricular (LV) function or clinical heart failure. These restrictions in use are the result of both early animal studies and numerous human investigations demonstrating myocardial depression from their negative chronotropic effects, β-receptor blockade and the membrane-stabilizing properties of certain agents.

HEMODYNAMIC EFFECTS OF BETA BLOCKERS IN ANIMAL MODELS

The hemodynamic changes observed during acute administration of propranolol[1–6] and sotalol[1–3,5–8] have been reported by several investigators. Intravenous sotalol (0.5 to 16 mg/kg) and propranolol (0.01 to 5 mg/kg) cause a dose-related decrease in rate-dependent parameters of myocardial contraction in animals,[1–3,6–8] although at any given heart rate sotalol appears to have less of a myocardial depressant effect.[1] In 1 study,[1] sotalol increased stroke volume (8 to 24%) at a similar LV end-diastolic pressure, whereas propranolol minimally changed stroke volume despite a significant increase in LV filling pressures. Because heart rate can dramatically alter myocardial contractility, the effects of propranolol (0.2 mg/kg) were studied by Whalen et al[4] over a range of fixed paced rates. Propranolol significantly decreased cardiac output, stroke volume and ejection fraction (EF) but increased end-systolic volume despite little change in mean blood pressure (afterload). This study, however, did not address the relative contribution of β-receptor blockade, per se, and any other intrinsic drug effect on the hemodynamic changes observed with propranolol.

In an attempt to clarify this issue, Aberg et al[5] reported the effects of intravenous sotalol and propranolol in the cat. Sotalol significantly decreased mean blood pressure and heart rate but had little effect on cardiac output because of an increase in stroke volume. Propranolol likewise decreased blood pressure and heart rate, but cardiac index decreased owing to a lack of increase in stroke volume. In the isolated cat papillary muscle, sotalol (0.1 mg/ml) did not diminish contractile force to electrical stimulation, whereas propranolol decreased contractile force by 32% at low (0.001 mg/ml) and up to 50% at higher (0.01 mg/ml) concentrations. Other investigators

have reported similar in vitro results.[9,10] These data would suggest that propranolol, unlike sotalol, has an intrinsic myocardial depressant action beyond its β-blocking properties. This conclusion has been further supported in dogs after catecholamine depletion with reserpine. In normal dogs, peak LV dP/dt decreases after administration of sotalol (1 to 6 mg/kg) despite cardiac pacing at a constant heart rate, and maintenance of a similar aortic pressure (afterload) and LV end-diastolic pressure (preload).[7] However, in catecholamine-depleted animals, sotalol does not decrease peak LV dP/dt beyond control values.[7] Hoffmann et al[6] compared the effects of propranolol (0.1 to 3.2 mg/kg) and sotalol (0.5 to 16 mg/kg) in normal dogs and in dogs that were given reserpine and paced at a constant heart rate. A dose-dependent decrease in contractile force (dF/dt) (Table I) was found with sotalol, although this was more pronounced after administration of equipotent doses of propranolol. Most of the decrease in contractile force observed in normal animals was abolished after reserpine administration, indicating that sotalol has minimal effects on contractility beyond its β-blocking properties. Although propranolol exhibited an independent myocardial depressant effect, this was observed predominantly at intravenous doses >1.6 mg/kg, which are several-fold higher than clinically administered doses.

These data have been extended to β blockers with intrinisic sympathomimetic activity. Goldstein et al[2] found a significant decrease in dF/dt over a range of decreasing heart rates with propranolol, sotalol and practolol in dogs pretreated with isoproterenol. However, in catecholamine-depleted animals, practolol increased while propranolol decreased dF/dt at doses >0.64 mg/kg. Fitzgerald et al[3] reported a consistent decrease in dP/dt after administration of propranolol, sotalol or practolol in dogs paced at fixed heart rates. However, in catecholamine-depleted animals, propranolol at doses >2.5 mg/kg continued to reduce dP/dt, whereas sotalol and practolol did not affect baseline dP/dt up to doses of 20 and 82 mg/kg, respectively.

HEMODYNAMIC EFFECTS OF BETA-BLOCKERS IN HUMANS

The hemodynamic effects of β blockers have been extensively reported in normal subjects and in patients with heart disease. Propranolol frequently is used as a prototype agent and has similar hemodynamic effects in humans and animals.

In normal subjects, propranolol[11–16] decreases heart rate moderately at rest (10 to 20%) and markedly during exercise. This heart rate reduction accounts in great part for the observed decline in rest and exercise cardiac index, although LV stroke volume also decreases (up to 22%).[12,14,16] Furthermore, propranolol (80 mg administered 4 times daily) significantly decreases upright rest and exercise radionuclide LVEF (−8 and −12%, respectively) concomitant with a significant increase in end-systolic volume (30 and 105%, respectively).[14] Similar declines in exercise LVEF after propranolol (100 mg 4 times daily) have been reported using supine gated radionuclide angiography (RNA), although rest LVEF is maintained. This suggests that β-adrenergic tone is more important in maintaining cardiac function while upright than during supine rest, but equally important in both body positions for augmenting cardiac function during exercise. Whether an intrinsic negative inotropic effect beyond β blockade contributes to these hemodynamic changes after propranolol has not been adequately addressed.

TABLE I Myocardial Contractile Force (Propranolol Versus Sotalol)

Dose (mg/kg)	Normal Dogs, Contractile Force (%)	Reserpinized Dogs, Contractile Force (%)
	Propanolol	
0	100	100
0.2	68.8 ± 10.3	87.0 ± 9.6
0.8	62.1 ± 12.9	82.0 ± 12.3
1.6	56.1 ± 15.3	71.8 ± 13.8
3.2	39.0 ± 14.2	54.7 ± 54.7
	Sotalol	
0	100	100
1.0	73.5 ± 19.3	92.0 ± 4.8
4.0	67.6 ± 15.6	90.4 ± 7.0
8.0	62.1 ± 17.7	84.5 ± 10.6
16.0	56.5 ± 17.8	81.1 ± 7.5

In patients with coronary artery disease who have no clinical heart failure,[12,17–22] intravenous (0.15 mg/kg) or oral (40 mg 4 times daily) propranolol reduces heart rate (5 to 22% and 7 to 29%) and cardiac output (15 to 27% and 16 to 25%) at rest and during exercise, respectively. Systolic blood pressure variably decreases at rest, and stroke volume[12,18,20–22] is consistently lower despite elevations in LV filling pressure.[12,18,21] In 1 report,[17] rest LVEF was maintained in patients with normal baseline cardiac function (LVEF of 53%) after propranolol (40 mg 4 times daily), but significantly decreased in those patients with prior infarction and depressed cardiac function (LVEF of 40%). This has also been reported by others.[15] Systemic vascular resistance increases due to the decline in cardiac output, and LV dP/dt decreases at rest and especially during exercise. Pulmonary artery pressure increases concomitantly with the increase in LV end-diastolic and pulmonary capillary wedge pressures.

Similar hemodynamic effects have been reported with other β blockers,[22–24] although agents with sympathomimetic properties do not appear to be myocardial depressants.[22–24] Taylor et al[23] reported comparable rest and exercise hemodynamic changes after administration of equipotent doses of intravenous propranolol (16 mg) and metoprolol (20 mg) in 24 patients with ischemic heart disease. Practolol (40 mg), however, had little effect on heart rate or blood pressure at rest, and caused less of a decrease in cardiac output during exercise than the other 2 agents.

In a study by Gebhardt et al,[24] a small series of patients with ischemic heart disease showed significantly less reduction in heart rate and blood pressure at rest with

TABLE II Hemodynamic Effects of Intravenous Sotalol at Rest

Investigator	Sotalol Dose (mg/kg)	Δ HR (%)	Δ SBP (%)	Δ MAP (%)	Δ SV (%)	Δ CO (%)	Δ SVR
Brooks, 1970*	0.4	↓20†	↓10†	↓5	↓ 4	↓19†	↑24†
Thumala, 1971*	0.1 to 0.5	↓15†	—	↑3	0	↓17†	↑15†
Hutton, 1972*	0.2	↓16†	↓ 9†	↓3	↓ 5	↓20†	↑19†
Kelly, 1978	0.06 to 0.26	↓ 4	—	0	↓10	↓ 9	—
Johnson, 1985‡	0.125 to 2.0	↓17†	↓13†	—	—	—	—
Astrom, 1986	0.6	↓16†	↓10†	—	↓11†	↓18†	—

* Ten minutes after administration.
† $p < 0.05$.
‡ Twenty minutes after administration.
CO = cardiac output; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; MAP = mean arterial pressure; SBP = systolic blood pressure; SV = stroke volume; SVR = systemic vascular resistance.

a greater increase in EF during exercise after receiving pindolol compared with propranolol. In a series of 6 patients with ischemic heart disease, Choong et al[22] studied the effects of propranolol and pindolol with rest and exercise gated RNA. Propranolol significantly decreased resting heart rate (18%), systolic blood pressure (10%), cardiac index (27%), stroke volume index (11%) and EF (5%). Systemic vascular resistance increased 24%, consistent with the decrease in cardiac output. End-systolic volume increased (12%), thus explaining the decrease in stroke volume index and EF. With exercise, heart rate (21%), systolic blood pressure (16%) and cardiac index (16%) also decreased compared with control values. However, due to a decline in end-systolic volume (8%), stroke volume and EF were maintained. The decline in end-systolic volume during exercise was presumed secondary to the anti-ischemic effects of propranolol. An improvement in exercise hemodynamics after propranolol in patients with ischemia during exercise has been reported by other investigators.[15,17] Pindolol also minimally decreased end-systolic volume (13%), so that stroke volume and EF were maintained. Thus, from these data, β blockers appear to depress LV function at rest, as evidenced by a decrease in stroke volume index and EF. Beta blockers with intrinsic sympathomimetic activity appear to have minimal effects on resting cardiac volumes or EF and may be more useful clinically in patients with depressed myocardial function.

Despite their measured depressant effects on cardiac function, β blockers are well tolerated in most patients, even those with a history of previous congestive heart failure. Extensive clinical experience from the large β-blocking trials in patients after myocardial infarction demonstrates their clinical safety.[25–28] The need to terminate drug therapy because of heart failure was similar in those patients taking placebo or β-blocking therapy. This was despite the frequent enrollment of patients with a history of congestive heart failure (18.5% in the BHAT trial).[25] Although recurrent heart failure was seen more frequently in those patients with prior congestive heart failure, it could usually be managed by intensifying medical therapy. Furthermore, the cumulative incidence of recurrent heart failure was similar in the propranolol and placebo groups. This is an important finding, since β-blocking therapy after myocardial infarction has been shown to reduce significantly the incidence of sudden cardiac death, particularly in patients with a history of previous heart failure. This reduction in mortality has not been shown using β blockers with intrinsic sympathomimetic activity.[29]

HEMODYNAMIC EFFECTS OF INTRAVENOUS SOTALOL IN HUMANS

The hemodynamic effects of intravenous sotalol are summarized in Table II. A significant decrease in heart rate and cardiac output usually occurs within 10 to 15 minutes of intravenous administration. The decrease in cardiac output is almost exclusively accounted for by the decrease in heart rate, since mean stroke volume is maintained. Pulmonary artery pressures do not appear to be elevated by the drug.

In normal volunteers, intravenous sotalol decreases heart rate and blood pressure during rest and exercise.[30,31] Hemodynamic changes for both parameters occur even at low doses of 0.125 mg/kg body weight. Frankl and Soloff[31] observed in normal healthy volunteers that at cumulative doses of 0.08 mg/kg, sotalol markedly blunted the effects of intravenous isoproterenol on heart rate, systolic blood pressure, cardiac index and stroke volume. However, no additional depression of cardiac function beyond the β-blocking effects of the drug was observed, implying no intrinsic negative effect on myocardial contractility.

Sotalol has also been studied in patients with heart disease. In an early report, Brooks et al[32] studied 20 patients with predominantly valvular heart disease who had at least class II New York Heart Association heart failure symptoms. LV end-diastolic pressure was initially elevated (>15 mm Hg) in 8 of 20 patients (40%) but did not significantly increase after sotalol administration. Astrom et al[33] studied the effects of intravenous sotalol in patients with acute myocardial infarction who had concomitant ventricular ectopy (>5 ventricular premature depolarizations per minute). In this placebo-controlled study, 10 patients received sotalol as an initial bolus of 0.5 mg/kg over 15 minutes followed by a loading infusion of 0.6 mg/kg over 1 hour, and a continuous infusion of 0.2 mg/kg for up to 12 hours. Heart rate decreased signifi-

cantly within 30 minutes after sotalol administration and remained consistently depressed throughout the infusion. Cardiac output and stroke volume decreased within 15 minutes after sotalol, but the former remained depressed throughout the infusion while the decrease in stroke volume was transient (up to 45 minutes). Minimal changes in right atrial and pulmonary artery pressures were observed. In this regard, intravenous sotalol was well tolerated in the setting of acute myocardial infarction. Similar results by other investigators[34] in patients with a variety of heart diseases have demonstrated no adverse effects of sotalol on pulmonary artery or pulmonary capillary wedge pressure during rest and exercise.

In a single-dose intravenous sotalol trial, Thumala et al[35] reported the hemodynamic changes at rest, during exercise and during atrial pacing in a patient population represented largely by coronary (42%) and rheumatic (29%) heart disease. Sotalol significantly decreased heart rate, cardiac index and LV dP/dt during rest, whereas LV end-diastolic pressure and systemic vascular resistance increased. Similar results were obtained during exercise but did not reach statistical significance because of the smaller number of patients and greater data variability. The decrease in cardiac index was thought to be secondary to bradycardia since resting and exercise stroke volume remained unchanged. The major determinants of myocardial contractility are preload, afterload, intrinsic contractility and heart rate. Because LV end-diastolic pressure (preload at rest) did not decrease and aortic pressure (afterload) remained unchanged, the observed decrease in dP/dt was postulated to be due to bradycardia and not to an intrinsic myocardial depressant action of the drug. However, when heart rate was fixed during atrial pacing, cardiac index (−20%), stroke volume index (−21%) and LV dP/dt (−13%) decreased despite little change in LV filling pressures. Hutton et al[36] also reported that cardiac pacing did not correct for the significant decrease in dP/dt in sotalol-treated patients. Despite the decrease in dP/dt, however, stroke volume was maintained in this study, probably owing to a concomitant decrease in blood pressure (afterload) that masked any decrease in myocardial contractility. The reported reduction in dP/dt would appear from animal investigations to be due to β-adrenergic blockade rather than to an intrinsic negative inotropic effect.

Intravenous sotalol, therefore, appears to affect cardiac hemodynamics within minutes of administration, which is heralded by a decrease in heart rate, systolic blood pressure and cardiac index. Stroke volume index is variably preserved depending on the relative contribution of negative inotropy and decreasing afterload.

HEMODYNAMIC EFFECTS OF ORAL SOTALOL

The hemodynamic effects after oral sotalol administration were recently evaluated in our laboratory as an ancillary study of a multicenter trial comparing the ventricular antiarrhythmic effects of sotalol and quinidine.[37] The study group consisted of 27 patients (18 men and 9 women, mean age 56 ± 12 years) with 30 or more ventricular premature depolarizations per hour on 24-hour Holter monitoring. Most of the patients (85%) had cardiac disease represented by coronary artery disease (14 patients), cardiomyopathy (4 patients), mitral valve prolapse (4 patients) and aortic insufficiency (1 patient). Thirteen patients had previous myocardial infarction and 9 had a history of congestive heart failure.

The study was a double-blind, placebo-controlled, crossover trial in which hemodynamic measurements were obtained after a 1-week placebo run-in period, after 4 weeks of drug 1, a second 2-week placebo phase, and after 4 weeks of drug 2. Hemodynamic measurements were obtained using gated RNA at rest and during supine bicycle exercise. Each patient exercised to an identical work load during all RNA studies so as to enable comparison of exercise hemodynamics from placebo to active sotalol administration. LV volumes, EF and cardiac output were measured by a count-based technique previously validated in our laboratory using gated blood pool RNA.[38]

Sotalol was given initially as a daily oral dose of 320 mg for 2 weeks, then increased to 640 mg/day if ventricular ectopy was not reduced by more than 75% from placebo baseline 24-hour Holter monitoring. Plasma sotalol levels were measured at the time of the gated RNA study. The mean peak and trough sotalol levels were 1,874 ± 1,099 and 1,545 ± 835 ng/ml, respectively, at a mean oral sotalol dose of 5.9 ± 2.3 mg/kg/day. In patients with adequate arrhythmia suppression, repeat RNA studies were obtained at 3 months and 1 year.

The mean baseline LVEF at rest was 43 ± 15%, with LVEF of <30% in 7 patients, 30 to 39% in 4 patients, 40 to 49% in 4 patients and >50% in 12 patients. Therefore, most of the patients (56%) had an abnormal LVEF at rest, 26% with severe LV dysfunction. No patient at the time of enrollment had clinical evidence of heart failure. Because patients with ventricular arrhythmia and depressed LV function are at the highest risk for subsequent sudden cardiac death, they would potentially benefit most from antiarrhythmic therapy. Thus, these patients represented an excellent target population for measuring the hemodynamic effects of sotalol.

The hemodynamic effects of sotalol are listed in Table III. Sotalol significantly reduced peak heart rate at rest and during exercise (23 and 20%, respectively) and systolic blood pressure at rest and during exercise (5 and 7%, respectively). Similar results have been reported by others after both intravenous and oral sotalol administration and presumably are the result of the β-adrenergic blocking effects of the drug. No change in diastolic or mean blood pressure was observed from placebo to active sotalol administration.

Sotalol significantly increased the mean group LVEF at rest with a trend toward an increase during exercise ($p < 0.08$). Furthermore, many patients (56%) had a >5% increase in absolute resting LVEF while taking sotalol. Only 1 of 7 patients with an LVEF <40% had a decrease in EF at rest during sotalol therapy.

LV volumes were significantly altered by sotalol. Mean LV end-diastolic volume at rest increased (13%),

TABLE III Hemodynamic Effects of Oral Sotalol

	Placebo		Sotalol	
	Rest	Exercise	Rest	Exercise
Heart rate (beats/min)	71 ± 11	117 ± 21	55 ± 8*	94 ± 21*
Systolic blood pressure (mm Hg)	132 ± 20	165 ± 21	125 ± 14†	154 ± 19†
Left ventricular ejection fraction (%)	47 ± 13	52 ± 15	51 ± 15‡	55 ± 14
End-diastolic volume index (ml/m^2)	111 ± 40	114 ± 46	125 ± 42†	120 ± 40
End-systolic volume index (ml/m^2)	63 ± 37	58 ± 41	65 ± 39	57 ± 33
Stroke volume index (ml/m^2)	48 ± 11	55 ± 15	59 ± 15*	63 ± 18
Cardiac index (liters/min/m^2)	3.4 ± 0.8	6.6 ± 2.3	3.3 ± 0.8	6.0 ± 2.2

* $p < 0.001$; † $p < 0.05$; ‡ $p < 0.002$.

with 65% of patients showing some increase in this parameter. The increase in LV end-diastolic volume was probably due to the indirect effect of bradycardia, which increased diastolic filling time, although a direct drug effect on LV compliance or an increase in LV filling pressures cannot be eliminated. Most of the patients (83%) had an increase in stroke volume index at rest (23%), which may have been secondary to changes in preload (increased LV end-diastolic volume), afterload (decrease in systolic blood pressure) or a direct positive inotropic effect. The last is unlikely because positive dP/dt has been shown to decrease after the administration of intravenous sotalol. Cardiac index at rest or during exercise did not change for the group as a whole, although there was marked individual variability depending on the differential increase and decrease in stroke volume and heart rate, respectively. In this regard, although all patients had a decrease in heart rate, only 48% of the patients studied had a >5% decrease in cardiac index at rest. When patients were stratified by baseline LVEF at rest, patients with LVEF of <40% did not demonstrate any greater untoward deterioration in any cardiac hemodynamic parameter than those patients with LVEF >40%.

The hemodynamic effects of oral sotalol (mean dose 754 ± 79 mg, range 230 to 1,200 mg/day) have also been reported in a single-blind trial involving 23 hypertensive patients.[39] A significant decrease in systolic blood pressure (212 ± 5 vs 189 ± 5 mm Hg; $p < 0.001$) and heart rate (87 ± 2 vs 62 ± 2 beats/min; $p < 0.001$) was observed, with the latter decreasing in all patients. Cardiac index tended to decrease for the group as a whole (3.15 ± 0.28 vs 2.73 ± 0.22; $p < 0.30$), although an increase was observed in 6 of 15 patients (40%). As in our study, stroke index significantly increased (34.4 ± 2.4 vs 46.6 ± 3.1; $p < 0.02$), indicating no overt negative inotropic effect.

Twelve of our patients who agreed to long-term sotalol therapy had gated RNA hemodynamic variables obtained at 3 months, as did 6 patients at 1 year. Six patients did not undergo 1-year studies because of loss of efficacy while taking sotalol (4 patients) and resolution of arrhythmia (2 patients). No patients were withdrawn from long-term sotalol because of cardiac decompensation. Patients remained otherwise clinically stable throughout the follow-up period while taking a mean sotalol dose of 370 mg/day. Although individual variability existed, mean blood pressure, cardiac volumes and cardiac index during rest and exercise were similar at 3 months and 1 year when compared with the hemodynamic data recorded during the acute sotalol dosing phase of the trial (Table IV). In this regard, long-term administration of sotalol did not appear to have a detrimental effect on cardiac function. Similarly, results of a recent double-blind, placebo-controlled, randomized trial of sotalol in patients after myocardial infarction did not indicate any increased incidence of clinical congestive heart failure over a 1-year period among treated patients.[28] Patients began therapy with sotalol (320 mg/day) 5 to 14 days after the initial infarction. Heart failure during the acute phase of infarction was present in 21 and 22% of those patients randomized to placebo and sotalol, respectively. During the follow-up period, heart failure developed in

TABLE IV Hemodynamic Effects of Oral Sotalol (Long-Term Results)

	Sotalol (Initial)		Sotalol (3 Months)		Sotalol (1 Year)	
	Rest (n = 12)	Exercise (n = 12)	Rest (n = 12)	Exercise (n = 8)	Rest (n = 6)	Exercise (n = 6)
HR (beats/min)	51 ± 6	87 ± 84	57 ± 7*	87 ± 11	56 ± 14	81 ± 13
SBP (mm Hg)	124 ± 17	149 ± 21	132 ± 23	155 ± 21	128 ± 28	149 ± 23
LVEF (%)	52 ± 13	54 ± 13	52 ± 12	51 ± 12	51 ± 10	55 ± 10
EDVI (ml/m^2)	119 ± 36	129 ± 38	113 ± 39	120 ± 35	123 ± 24	125 ± 22
ESVI (ml/m^2)	58 ± 29	62 ± 34	57 ± 29	62 ± 47	60 ± 22	56 ± 17
SVI (ml/m^2)	61 ± 15	66 ± 15	56 ± 16	57 ± 26	62 ± 13	69 ± 17
CI (liters/min/m^2)	3.1 ± 0.8	5.9 ± 2.1	3.1 ± 0.8	5.1 ± 2.1	3.5 ± 1.0	5.6 ± 2.0

* $p < 0.05$.
CI = cardiac index; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; LVEF = left ventricular ejection fraction; SVI = stroke volume index; other abbreviations as in Table II.

TABLE V Hemodynamic Profile of Patients With and Without Serious Complications Taking Sotalol

	No Complications (n = 20)		Complications (n = 5)	
	Rest	Exercise	Rest	Exercise
End-systolic volume index (ml/m²)	60 ± 37	59 ± 43	102 ± 57*	91 ± 51
Left ventricular ejection fraction (%)	48 ± 13	53 ± 15	35 ± 14	36 ± 14*
Cardiac index (liters/min/m²)	3.4 ± 0.8	6.8 ± 2.2	3.2 ± 1.0	4.6 ± 1.4*
Stroke volume index (ml/m²)	49 ± 11	57 ± 14	48 ± 13	44 ± 10†

* $p < 0.05$; † $p < 0.051$.

3.8% of placebo- and in only 2.6% of sotalol-treated patients (difference not significant).

In our study, 5 patients had serious complications while taking sotalol during the initial double-blind phase of the trial. Three patients had dysrhythmias, which included torsades de pointes ventricular tachycardia, ventricular fibrillation, and syncope due to hypotension and bradycardia. The 2 patients (7%) in whom overt congestive heart failure developed while taking sotalol were noted to have low LVEFs at rest (18 and 23%) and markedly dilated LV chambers (end-diastolic volume indexes greater than 200 ml/m²). Sotalol drug levels were not different in the patients with or without complications, although the patient numbers were too small to dismiss categorically a dose effect.

The 5 patients with serious complications during sotalol administration had a different hemodynamic profile during placebo administration from that found for the remaining 20 patients who tolerated sotalol well. These 5 patients were found to have a higher LV end-systolic volume index at rest, were unable to achieve an increase in LVEF or stroke volume index during exercise, and had a minimal increase (<1.3 liters/min/m²) in cardiac index during exercise (Table V). Hemodynamics at rest were imprecise in identifying patients who would have an adverse outcome with sotalol. This was particularly true for LVEF at rest, since only one-third of the patients with LVEF <30% had congestive heart failure or arrhythmia aggravation. Likewise, although the sensitivity of an abnormal (<5%) increase in LVEF during exercise identified all patients with complications, this was accompanied by a very low specificity of 45% (Table VI). This hemodynamic profile of inadequate cardiac reserve during supine bicycle exercise for predicting complications during drug therapy extends our previous observations with 2 other antiarrhythmic drugs, moricizine[40] and cibenzoline.[41] Therefore, sotalol is generally well tolerated, with the possible exception of those patients whose hemodynamic parameters reflect markedly depressed LV function and inadequate cardiac reserve. Patients with these hemodynamic parameters may be very dependent on β-adrenergic drive to maintain cardiac function, the latter being significantly attenuated during sotalol administration.

TABLE VI Sensitivity, Specificity and Predictive Value of Baseline Hemodynamic Measurements in Determining Serious Complications of Sotalol Treatment

	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Fisher Exact Test (p value)
Δ LVEF <5%	100	45	31	100	0.12
Δ SVI <0	80	85	57	94	0.01
Δ CI <1.3	80	90	67	95	0.006
Δ SVI <0 and Δ CI <1.3	80	100	100	95	0.001

Δ = change from rest to exercise while taking placebo preceding sotalol. Abbreviations as in Table IV.

CONCLUSION

Beta-receptor blocking agents depress cardiac function by decreasing heart rate and β-adrenergic drive, and through an intrinsic membrane-stabilizing effect observed with certain agents. Although the latter appears important in the animal model, the doses needed to produce this effect are generally far above the usual clinical range. Nevertheless, β blockers such as propranolol decrease EF, stroke volume, heart rate and cardiac output at rest and during exercise in both normal subjects and patients with heart disease.

Sotalol appears to have less of a myocardial depressant effect than conventional β blockers. After intravenous administration, heart rate, cardiac output and systolic blood pressure decrease, although stroke volume is generally maintained. Sotalol is well tolerated when given orally to patients with heart disease and mildly depressed cardiac function. However, occasionally it may cause clinical signs of heart failure. This is typically seen in patients with inadequate cardiac reserve and markedly depressed LV function. There appear to be no ill effects on cardiac function from long-term sotalol use. A comparative trial between sotalol and traditional β-blocking agents are needed to better define their hemodynamic differences in the same patients at equipotent β-blocking doses of each drug.

REFERENCES

1. Gomoll AS, McKinney GR. Sotalol: cardiac and hemodynamic actions in the anaesthetized dog. In: Snart AG, ed. Advances in Beta-Adrenergic Blocking Therapy—Sotalol. *Amsterdam: Excerpta Medica, 1974:6–22.*

2. Golstein RE, Hall CA, Epstein SE. Comparison of relative inotropic and chronotropic effects of propranolol, practolol, and sotalol. *Chest 1973;64:619–627.*

3. Fitzgerald JD, Wale JL, Austin M. The haemodynamic effects of (±) propranolol, dexpropranolol, oxprenolol, practolol and sotalol in anaesthetised dogs. *Eur J Pharmacol 1972;17:123–134.*

4. Whalen RE, Morris JJ, Behar VS, McIntosh HD. Hemodynamic effects of beta-adrenergic blockade at controlled ventricular rates. *Am Heart J 1968; 76:775–783.*

5. Aberg G, Dzedin T, Lundholm L, Olsson L, Svedmyr N. A comparative study

of some cardiovascular effects of sotalol (MJ 1999) and propranolol. *Life Sci 1969;8:353–365.*

6. Hoffmann RP, Grupp G. The effects of sotalol and propranolol on contractile force and atrioventricular conduction time of the dog heart in situ. *Dis Chest 1969;55:229–234.*

7. Dexter L, Brooks H, Banas JS, Meister S, Szucs MM, Dalen JE. Effects of sotalol on myocardial function in dogs and in patients with heart failure. In: Snart AG, ed. Advances in Beta-Adrenergic Blocking Therapy—Sotalol. *Amsterdam: Excerpta Medica, 1974:41–55.*

8. Puri PS, Bing RJ. Effects on myocardial contractility, hemodynamics and cardiac metabolism of a new beta-adrenergic blocking drug, sotalol. *Dis Chest 1969;55:235–239.*

9. Levy JV, Richards V. Inotropic and metabolic effects of three beta-adrenergic receptor blocking agents on isolated rabbit left atria. *J Pharmacol Exp Ther 1965;150:361–369.*

10. Parmley WW, Chuck LH. Lack of intrinsic myocardial depressant effects of the beta blocker sotalol (MJ-1999) as compared to propranolol (abstr). *Circulation 1970;42:suppl III:III-188.*

11. Epstein SE, Robinson BF, Kahler RL, Braunwald E. Effects of beta-adrenergic blockade on the cardiac response to maximal and submaximal exercise in man. *J Clin Invest 1965;44:1745–1753.*

12. Parker JO, West RO, DiGiorgi S. Hemodynamic effects of propranolol in coronary heart disease. *Am J Cardiol 1968;21:11–19.*

13. Epstein SE, Braunwald E. Beta-adrenergic receptor blocking drugs: mechanisms of action and clinical applications. *N Engl J Med 1966;17:1106–1112.*

14. Port S, Cobb FR, Jones RH. Effects of propranolol on left ventricular function in normal man. *Circulation 1980;61:358–366.*

15. Marshall RC, Wisenberg G, Schelbert HR, Henze E. Effect of oral propranolol on rest, exercise and postexercise left ventricular performance in normal subjects and patients with coronary artery disease. *Circulation 1981;63:572–583.*

16. Robin E, Cowan C, Puri P, Ganguly S, DeBoyrie E, Martinez M, Stock T, Bing RJ. A comparative study of nitroglycerin and propranolol. *Circulation 1967;36:175–183.*

17. Rainwater J, Steele P, Kirch D, LeFree M, Jensen D, Vogel R. Effect of propranolol on myocardial perfusion images and exercise ejection fraction in men with coronary artery disease. *Circulation 1982;65:77–81.*

18. Wiener L, Dwyer EM, Cox JW. Hemodynamic effects of nitroglycerin, propranolol, and their combination in coronary heart disease. *Circulation 1969;39:623–631.*

19. Haerem JW, Westheim A, Fonstelien E. Acute hemodynamic effects of propranolol, glycerylnitrate, and exercise in coronary patients with left ventricular dysfunction. *Int J Cardiol 1985;9:465–475.*

20. Dwyer EM, Wiener L, Cox JW. Effects of beta-adrenergic blockade (propranolol) on left ventricular hemodynamics and the electrocardiogram during exercise-induced angina pectoris. *Circulation 1968;38:250–259.*

21. Lewis CM, Brink AJ. Beta adrenergic blockade: hemodynamics and myocardial energy metabolism in patients with ischemic heart disease. *Am J Cardiol 1968;21:846–858.*

22. Choong CY, Roubin GS, Harris PJ, Tokuyasu Y, Shen W, Bautovich GJ, Kelly DT. A comparison of the effects of beta-blockers with and without intrinsic sympathomimetic acitivity on hemodynamics and left ventricular function at rest and during exercise in patients with coronary artery disease. *J Cardiovasc Pharmacol 1986;8:441–448.*

23. Taylor SH, Silke B, Lee PS. Intravenous beta-blockade in coronary heart disease: is cardioselectivity or intrinsic sympathomimetic activity hemodynamically useful? *N Engl J Med 1982;306:631–635.*

24. Gebhardt VA, Wisenberg G, Mitton K, Prato F. The influence of intrinsic sympathomimetic activity in preserving left ventricular function in ischemic heart disease (abstr). *JACC 1983;1:709.*

25. Chadda K, Goldstein S, Byington R, Curb JD. Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. *Circulation 1986;73:503–510.*

26. The Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med 1981;304:801–807.*

27. Friedman LM. How do the various beta blockers compare in type, frequency and severity of their adverse effects? *Circulation 1983;67:suppl I:I-89–I-90.*

28. Julian DG, Prescott RJ, Jackson FS, Szekely P. Controlled trial of sotalol for one year after myocardial infarction. *Lancet 1982;1:1142–1147.*

29. Australian and Swedish Pindolol Study Group. The effect of pindolol on the two year mortality after complicated myocardial infarction. *Eur Heart J 1983;4:367–375.*

30. Johnston GD, Finch MB, McNeill JA, Shanks RG. A comparison of the cardiovascular effects of (+)-sotalol and (±)-sotalol following intravenous administration in normal volunteers. *Br J Clin Pharmacol 1985;20:507–510.*

31. Frankl WS, Soloff LA. Sotalol: a new, safe beta adrenergic receptor blocking agent. *Am J Cardiol 1968;22:226–272.*

32. Brooks H, Banas J, Meister S, Szucs M, Dalen J, Dexter L. Sotalol-induced beta blockade in cardiac patients. *Circulation 1970;42:99–110.*

33. Astrom M, Edhag O, Nyquist O, Vallin H. Haemodynamic effects of intravenous sotalol in acute myocardial infarction. *Eur Heart J 1986;7:931–936.*

34. Kelly JJ. Evaluation of sotalol hydrochloride, given intravenously on the hemodynamic responses of patients with normal hearts, trivial heart disease, tachycardia and excessive sympathetic stimulation. *Mead Johnson Research Center Project 1999/IND 2544, June 1, 1978.*

35. Thumala A, Hammermeister KE, Campbell WB, Pomerantz B, Overy H, Davies H. Hemodynamic studies with sotalol in man, performed at rest, during exercise, and during right ventricular pacing. *Am Heart J 1971;82:439–447.*

36. Hutton I, Lorimer AR, Hillis WS, McCall D, Reid JM, Lawrie TD. Haemodynamics and myocardial function after sotalol. *Br Heart J 1972;34:787–790.*

37. Mahmarian JJ, Verani MS, Hohmann T, Hill R, Thornton BC, Bolli R, Young JB, Roberts R, Pratt CM. The hemodynamic effects of sotalol and quinidine: analysis of use of rest and exercise gated radionuclide angiography. *Circulation 1987;76:324–331.*

38. Verani MS, Gaeta J, LeBlanc AD, Poliner CR, Phillips L, Lacy JL, Thornby JI, Roberts R. Validation of left ventricular volume measurements by radionuclide angiography. *J Nucl Med 1985;26:1394–1400.*

39. Verniory A, Staroukine M, Delwiche F, Telerman M. Effect of sotalol on haemodynamics and reinin-angiotensin-aldosterone system in hypertensive patients. *Clin Sci Mol Med 1976;51:9–17.*

40. Pratt CM, Wierman A, Seals AA, English L, Leon C, Young JB, Quiniones MA, Roberts R. Efficacy and safety of moricizine in patients with ventricular tachycardia: results of a placebo-controlled prospective long-term clinical trial. *Circulation 1986;73:718–726.*

41. Seals AA, Haider R, Leon C, Francis M, Young JB, Robert R, Pratt CM. Antiarrhythmic efficacy and hemodynamic effects of cibenzoline in patients with nonsustained ventricular tachycardia and left ventricular dysfunction. *Circulation 1987;75:800–808.*

Discussion I: Pharmacology, Pharmacodynamics and Pharmacokinetics of Sotalol

Dr. Bramah Singh (Los Angeles, California): Dr. Antonaccio, you gave a comprehensive presentation on the pharmacodynamics and pharmacokinetics of sotalol. Is sotalol removed from the blood during hemodialysis?

Dr. Michael Antonaccio (Wallingford, Connecticut): I am not aware that the drug is dialyzed in this way. Perhaps Dr. Lester Soyka can comment on this issue.

Dr. Lester Soyka (Wallingford, Connecticut): There was an unreported study from the group in Indianapolis that suggested that sotalol is dialyzed.

Dr. Magdi Sami (Montreal, Quebec, Canada): One of my patients was well controlled on a given dose of sotalol for recurrent paroxysmal atrial flutter, atrial fibrillation, and ventricular arrhythmias. As long as he had chronic renal failure with serum creatinine levels around 5 and 6 μg/ml, he was doing extremely well. We began hemodialysis, and each time—either during or just after dialysis—his arrhythmia broke through with very rapid rates. Without knowing whether or not sotalol did go through the dialysis membrane, we administered an extra dose of sotalol just before dialysis. Thereafter, his arrhythmia was completely controlled. This, I believe, is a good basis for thinking that sotalol does pass through the dialysis membrane.

Question: Concerning the frequency-dependent effect on the action potential duration, sotalol appears to behave exactly like quinidine in this regard, but it does not block the inactivated sodium current. Is there a similarity between the action of amiodarone and that of sotalol?

Dr. Singh: I do not think so. The electrophysiologic effects of amiodarone are unique. The effects of sotalol and quinidine on ionic currents in repolarization are probably different, but it will take a great deal of detailed single-channel studies in isolated ventricular myocytes to delineate the nuances of differences. This must await the results of future studies.

Dr. James Reiffel (New York, New York): Dr. Antonaccio, you showed some very good studies of pretreatment with blockers in terms of changes in repolarization. Could you tell us anything about pretreatment with either calcium-channel blockers or digitalis that may be clinically relevant in terms of co-administration of drugs?

Dr. Antonaccio: Dr. Lathrop has studied calcium-channel blockers with respect to this action on lengthening the action potential duration.

Dr. David Lathrop (Cincinnati, Ohio): We have not looked at the effects of co-administration of sotalol and nifedipine, or other dihydropyridines. In fact, we found highly variable effects with other calcium antagonists. Often, the presence of sotalol, while giving calcium-channel blockers, increases rather than decreases the action potential duration. I do not know what this means, but I suspect that sotalol has no effect at all on calcium-channel directly.

Dr. Singh: There are some relevant data from Dr. Joel Kupersmith. Hiramasu et al[1] showed that if you take isolated cardiac tissue superfused with d-sotalol in large concentrations, there is massive lengthening of the action potential duration with a tendency for the development of early afterdepolarizations. This was prevented by the co-administration of the calcium-channel blocker verapamil, which shortened the action potential duration. I think that data are rather dramatic, at least in vitro. I am not sure how this will apply in vivo. If it holds up, it has important therapeutic implications in that a combination of calcium-channel blockers and QT-lengthening compounds may be associated with the lower-than-expected incidence of torsades de pointes.

Question: I also asked about digitalis, because we have seen the additive clinical effects of d-sotalol and digitalis in patients for whom digoxin alone did not work, and yet the combination with sotalol was clearly effective in atrial arrhythmias.

Dr. Singh: We need more systematic data on this issue. Moving on now to Dr. Woosley's interesting data, Dr. Woosley raised an intriguing possibility in the relationship between the effects of action potential lengthening and slowing of the heart rate. After all, such a change only in the sinus node potential could make a difference. If the effect of the drug is minimal on the duration of the sinus node potential, and if the sinus is being driven at a higher rate, it will override the subsidiary pacemakers. Clearly, the sinus frequency will have a major effect on the QTc. I am therefore uncertain how one can relate a bradycardic response in the sinus node produced by the lengthening of the action potential duration in the ventricle. One probably needs a substantial increase in the duration of the sinus node potential itself as a primary event to have a modest effect on heart rate.

Dr. Raymond Woosley (Washington, D.C.): The basic tenet of this matter is that the surface QT is (or changes therein are) proportional to changes in the sinoatrial node/QT relationship, and our data are consistent with that. It certainly does not prove it. Data in the literature indicate that, in animal in vitro studies, the sinus node action potential duration is proportional to the QTc on the surface electrocardiogram. So I think it is consistent with what we have reported but, as you suggested, this can never be proved because it is measured on the surface electrocardiogram, and until someone implants a microelectrode in a patient's sinus node and relates the changes in repolarization in that structure to the resultant heart rate, our hypothesis cannot be validated with certainty.

Dr. Singh: You will also need simultaneous recordings of the ventricular monophasic potentials. Over the years, with a number of colleagues, we have made numerous transmembrane potential recordings from the rabbit sinus node and have related them to simultaneous changes

in the ventricular myocardium. In the case of the sinus node, with superfusion of the preparation with d-, l- and dl-sotalol[2] and in chronically "amiodaronized" animals, the action potential duration increases only moderately, while the action potential duration changes in the ventricular myocardium, the essential correlate of alterations in the QT, are often striking and considerable.[3] I have speculated that the relative "resistance" of the sinoatrial node potential to lengthening in response to agents that have a marked prolonging effect on the action potential duration in atria and ventricles might have survival value. The other issue is whether high concentrations of d-sotalol produce some β-blocking effect that contributes to the bradycardic effects of d-sotalol.

Dr. Woosley: This is what we were trying to address. The point I failed to make was that there was not a significant change in blood pressure with d-sotalol, which might indicate that β blockage was not responsible. Recent formulations of d-sotalol in formal testing have been shown to have very little β-blocking effect.

Dr. Antonaccio: With respect to the potential positive inotropic effect induced by sotalol in vitro, it has been pointed out that this is directly related to the increase in the action potential duration. Clinically, that might translate into the prolongation of the QTc interval. Dr. Mahmarian, did you examine the prolongation of QTc in relation to hemodynamic effects in your patients?

Dr. John Mahmarian (Houston, Texas): No, we did not look at QTc values.

Dr. Prakash Deedwania (Fresno, California): You mentioned an increase in the left ventricular ejection fraction. We know that sotalol decreases heart rate very significantly, and you also indicated that the end-systolic volume index did not change. There was no increase in cardiac index but stroke volume increased, as might be expected if heart rate decreases. We know that when we increase stroke-volume index by slowing the heart rate, we need to correct it to allow us to compare values before and after therapy. Did you correct it for heart rate?

Dr. Mahmarian: We did not correct it for heart rate, but I agree with you that the increased end-diastolic volume index was probably due to bradycardia and would increase stroke volume at any given end-systolic volume.

Dr. Deedwania: If you carefully scrutinize your end-systolic volume index, it might remain the same.

Dr. Mahmarian: That is correct. The increase in stroke volume index resulted mainly from the increased end-diastolic volume index.

Question: Your measurements of radionuclide ventriculogram–derived variables are good in the sense that they are easy to obtain and relatively precise, but they do not necessarily translate directly into how patients tolerate drugs. Do you have any data in patients treated with antiarrhythmic drugs on how they might influence cardiopulmonary exercise testing where the end points of testing are variables, such as oxygen consumption and anaerobic threshold?

Dr. Mahmarian: No. In this particular study, in all patients, the work load was kept identical from placebo to drug, but we do not have data on oxygen consumption or anaerobic threshold in these patients.

Dr. Singh: We have heard that sotalol may exert a positive inotropic effect in certain circumstances, and it appears to have fewer negative inotropic effects than conventional β blockers. Regarding the relationship between effects of class III agents and inotropy in general, it is of interest that most, if not all, class III drugs exert a positive inotropic effect that is most readily shown in isolated tissues and preparations. However, in the case of sotalol, we are dealing with a complex balance between β blockade and a positive inotropic effect in a single agent. Depending on the prevailing conditions in the individual patient, you may see a depressant effect, no effect, or a frankly positive inotropic effect, as well as their hemodynamic correlates. However, there is no doubt that compared with a typical β blocker, at least in our experience and in the experience of most people from whom you have heard, sotalol really has fewer depressant effects than you might expect given the degree of β blockade. I think this point emerges fairly clearly from the data presented. It is of practical importance that most serious life-threatening ventricular arrhythmias occur in patients with compromised ventricular performance, and there are increasing data implicating the potential role of the adrenergic nervous system in the genesis of such arrhythmias.

Dr. Mahmarian: If you look at the patients who did develop complications in terms of heart failure, as I said, they had marginally depressed function. They had large end-systolic volumes. They were probably those patients who had increased sympathetic tone to begin with, although we did not measure this, in terms of circulating catecholamines. This might be why they had hemodynamic deterioration resulting from β-blocking effects. Again, sotalol does not exhibit baseline intrinsic negative inotropic effects and if it does decrease myocardial function, it is probably due to β blockade as the sole mechanism.

Dr. Singh: I agree. The net response might be influenced by how critically the ventricular function depends on the adrenergic drive for hemodynamic compensation.

We have heard a great deal about the unique properties of sotalol as a β blocker and a class III antiarrhythmic drug. The next series of papers will deal with the data on the antiarrhythmic effects of the compound.

REFERENCES

1. Hiramasu S, Coto H, Li Z-Y, Maldonado C, Kupersmith J. Dextro rotary isomer of sotalol. Electrophysiologic effects and interaction with verapamil. *Am Heart J 1988;116:1552–1557.*

2. Kato R, Ikeda N, Yabek SM, Kannan R, Singh BN. Electrophysiologic effects of the levo- and dextro rotary isomers of sotalol in isolated cardiac muscle and their in vivo pharmacokinetics. *JACC 1986;7:116–125.*

3. Ikdea N, Nademanee K, Kannan R, Singh BN. Electrophysiologic effects of amiodarone: experimental and clinical observations relative to serum and tissue concentrations. *Am Heart J 1984;108:890–898.*

Effectiveness of Sotalol for Therapy of Complex Ventricular Arrhythmias and Comparisons with Placebo and Class I Antiarrhythmic Drugs

Jeffrey L. Anderson, MD

In new antiarrhythmic drug development, key comparisons include those with placebo, standard (class I) agents and other β blockers. This review will cover the first 2 comparisons. The effectiveness of 2 doses of sotalol for complex ventricular arrhythmias has been compared with placebo in a 6-week, multicenter study (parallel, double-blind design) in 102 patients. The frequency of ventricular premature complexes (VPCs) was reduced only 10% with placebo, 75% with low-dose sotalol (160 mg administered twice daily) and 88% with high-dose sotalol (320 mg administered twice daily) (both p <0.05 vs placebo). The defined efficacy criterion (≥75% VPC suppression) was achieved by 6% of patients taking placebo, 34% of patients taking low- and 71% of patients taking high-dose sotalol. Sotalol was generally well tolerated, especially with the lower dose. Heart rate decreased, and PR and QTc intervals increased modestly. An open, randomized, crossover study compared sotalol with procainamide in 33 patients. A reduction in VPCs of ≥75% was achieved in 22 patients (67%) with sotalol and in 13 patients (39%) with procainamide. Quinidine and sotalol have also been compared in a multicenter study in patients with chronic, complex VPCs, with results to be presented in the near future. Thus, sotalol's antiarrhythmic efficacy is well demonstrated by comparisons with placebo, and its effectiveness and tolerance are likely to compare favorably with standard class I drugs, suggesting its potential as a first-line antiarrhythmic agent.

(Am J Cardiol 1990;65:37A–42A)

From the Department of Medicine, University of Utah, Salt Lake City, Utah.

Address for reprints: Jeffrey L. Anderson, MD, Division of Cardiology, LDS Hospital, Eighth Avenue and C Street, Salt Lake City, Utah 84143.

Since 1977, the United States Food and Drug Administration has approved and labeled 5 class I antiarrhythmic drugs (disopyramide, tocainide, mexilitene, flecainide and encainide), several class II drugs (β-adrenergic blockers), but only 1 class III agent (amiodarone), which is limited in its application because of its high inherent toxic potential. Sotalol, a β blocker with additional characteristics of a class III antiarrhythmic agent, will be a unique and welcomed addition to these new agents.[1–3] It is an old compound recently rediscovered as a potentially important new antiarrhythmic agent. Its historical development and electrophysiologic and pharmacologic findings have been presented elsewhere in the symposium.[4–5] In this study, key comparisons that are important in new antiarrhythmic drug evaluation will be presented. These evaluations, specifically with respect to effects on chronic, complex ventricular arrhythmias, include (1) efficacy and tolerance comparison of sotalol with placebo; (2) comparisons of efficacy and side-effect potential with the "standard" (class I, membrane-active) antiarrhythmic agents (e.g., procainamide, quinidine); and (3) comparison with other conventional agents.[6] The results of these comparisons are necessary to establish a profile of the effectiveness and safety of sotalol and to suggest how it may be positioned in future medical practice for selection and use in treating these symptomatic and prognostically important arrhythmias.

This review covers evaluations using ambulatory electrocardiographic recording as the end point for antiarrhythmic drug response. In these ventricular ectopic studies, 24- to 48-hour ambulatory electrocardiographic (ECG) recordings were applied to evaluate baseline frequencies of ventricular premature complexes (VPCs), repetitive VPC frequencies (beats in couplets and runs), and ventricular tachycardia (VT) events (3 or more beats, rate ≥100 beats/min). In addition, symptomatic improvement with therapy was evaluated as a secondary efficacy end point. Criteria for safety in these studies included reporting of on-therapy conditions (potential adverse drug experiences), numbers of discontinuations of drug because of adverse effects, incidence of adverse rhythm events (potentially proarrhythmic), and occurrence of laboratory abnormalities, potentially indicating drug toxicity. Key comparative studies with placebo, procainamide and quinidine are summarized and the comparative value of sotalol reported. No systematic comparisons with other class I agents (IB and IC) or other class III agents have been reported.

TABLE I Patient Characteristics

Variable	Placebo (n = 37)	Sotalol (320 mg/day) (n = 38)	Sotalol (640 mg/day) (n = 39)
Age (years)	58 ± 14	57 ± 14	61 ± 13
Sex (% male)	65	71	72
Coronary artery disease (%)	37	36	38
Hypertension (%)	35	39	56
VPCs/hour (mean)	343	382	352
Ejection fraction (%)	53 ± 9	51 ± 10	55 ± 10

VPCs = ventricular premature complexes.

COMPARISON OF SOTALOL AND PLACEBO IN PATIENTS WITH FREQUENT AND REPETITIVE VENTRICULAR ECTOPIC ACTIVITY: MULTICENTER COMPARATIVE STUDY

Methods: Sotalol has been compared with placebo in a multicenter comparative study in patients with frequent and repetitive ventricular activity. An initial report summarized results in 56 completing patients.[7] The present update summarizes results in the entire complete group of 102 patients.[8]

Purpose and design: The purpose of this study was to document the antiarrhythmic effectiveness and tolerance of 2 doses of sotalol (320 and 640 mg/day) compared with placebo for suppression of chronic, complex ventricular arrhythmias in patients requiring treatment. To accomplish this goal, the study was designed as a parallel, double-blind trial of 6 weeks' duration in 6 hospitals consisting of the following phases: (1) Week 1 formed the screening, baseline phase, consisting of 48 hours of ambulatory recording in the absence of antiarrhythmic agents (>5 half-lives washout). (2) Week 2 consisted of a baseline placebo phase that was single-blind; 48 consecutive hours of ambulatory monitoring were recorded and used to qualify patients for randomization into the double-blind phase. (3) The third phase (active treatment) began with randomization in week 3 and concluded in week 6. It was divided into early and final treatment-assessment phases. Initial treatment was assessed on day 2 or 3 (after 2 to 6 doses of drug given in divided doses twice daily) and consisted of a 24-hour ambulatory tape. The final assessment was made during week 6 and consisted of a 48-hour ambulatory recording. The randomization code was then broken, and the option of long-term open-label treatment with sotalol was considered, based on the clinical assessment of the investigator.

Entry criteria: Eligibility criteria included age ≥18 years, spontaneous rate of ventricular arrhythmias of ≥30 VPCs/hour for 48 hours on screening and placebo and baseline studies, and arrhythmia judged to require therapy based on symptoms or prognostic importance.

Exclusion criteria included: advanced heart failure (New York Heart Association class IV) or an ejection fraction of <30%; a history of β-blocker intolerance, asthma or symptomatic obstructive pulmonary disease and electrolyte imbalance; renal dysfunction (creatinine >3 mg/dl); severe, untreated hypertension (diastolic blood pressure ≥120 mm Hg); and unstable clinical status, such as unstable angina or recent myocardial infarction (≤3 months).

Rhythm exclusions included an average heart rate at rest of <50 beats/min, sinus node disease (pauses >2.5 seconds), atrioventricular node disease (second- or third-degree atrioventricular block), a long QT interval syndrome (QTc >0.45 second), or prolongations of PR interval (>0.24 second) or QRS interval (>0.18 second). In addition, patients with a history of sustained, malignant ventricular arrhythmia were excluded (history of sustained VT lasting over 30 seconds or a history of primary ventricular fibrillation, unrelated to acute myocardial infarction).

Patient characteristics and study flow: A total of 178 patients underwent screening ambulatory monitoring for the study, and 126 qualified for and entered the single-blind placebo baseline period. Of these, 114 met criteria for randomization (≥30 VPCs/hour) and entered the double-blind treatment period. A total of 102 patients could be assessed for efficacy, 96 for the initial ("first pass") period, and 92 for the final efficacy period. All 114 patients entering double-blind treatment were assessed for safety. Patient entry characteristics were similar for the 3 study groups and are presented in Table I.

Efficacy results: A successful efficacy result was defined as a ≥75% reduction in total VPCs per hour or a ≥90% reduction in repetitive ectopy per hour or VT events per day on the final (6-week) Holter recording, compared with the placebo-baseline study. Total VPCs per hour were reduced only 10% with placebo, 75% with sotalol, 160 mg twice daily (320 mg/day) ($p < 0.05$ vs placebo), and 88% with sotalol, 320 mg twice daily (640 mg/day) ($p < 0.05$ vs placebo and sotalol 320 mg/day) (Fig. 1, Table II). The corresponding percentages of patients achieving the 75% efficacy level were as follows: placebo, 6%; low-dose sotalol, 34% ($p < 0.05$); and high-dose sotalol, 71% ($p < 0.05$ vs placebo and low-dose) (Fig. 1, Table II).

Significant differences between placebo and sotalol were also evident for percent reductions in repetitive ectopy per hour and VT events per day (Table II), although there was lower power to assess effects due to lower and more variable frequencies of VT events per day and greater variability in response. In general, however, repetitive ectopy was suppressed to a greater degree than total VPCs per hour for low-dose sotalol, but no additional advantage of higher dose sotalol was observed.

The effectiveness of sotalol was already well established by the initial (day 2 to 3) Holter monitoring, which showed similar percent VPC reductions from baseline and patient response rates as the final treatment Holter monitoring for low-dose sotalol and only a slightly lower response as the week 6 Holter monitoring for high-dose sotalol (percent reduction, 85 vs 88%; response rates, 53 vs 71%).

In the baseline state, the study group showed a diurnal variation in average VPC frequency, with increasing rates during waking hours (6 A.M. to midnight), with peak

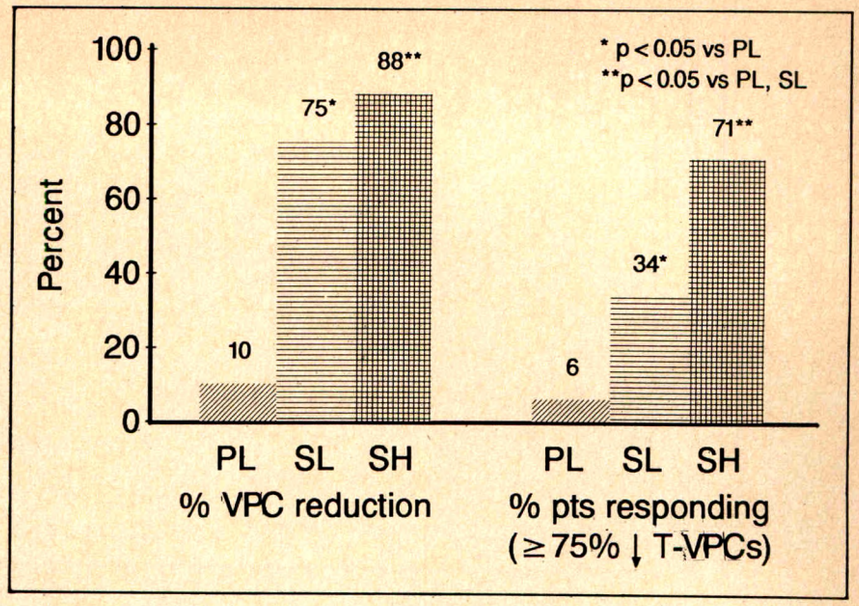


FIGURE 1. Comparative responses of total ventricular premature complexes (VPCs) per hour to sotalol and placebo. *Left,* response in percent VPC reduction presented for placebo (PL), sotalol, low-dose (SL) and sotalol, high-dose (SH) groups. (p values of the continuous VPC variables were based on the analysis of variance of the log-transformed values.) *Right,* patient response rate (% patients with ≥75% suppression, comparing baseline and 6-week recordings) presented for the 3 groups.

frequency between 10 A.M. and 6 P.M., and decreased rates during sleep hours (midnight to 6 A.M.). This diurnal variation was substantially blunted by sotalol (Fig. 2).

Effects on electrocardiographic intervals: Sotalol caused the expected changes in ECG intervals. Typical of therapy with a β blocker, heart rate was reduced; reductions were similar for both doses of sotalol (−18 and −17 beats/min, respectively) compared with placebo (−1 beat/min, $p < 0.001$ vs either dose of sotalol). Similarly, as expected, there were modest increases in PR interval (+7 and +10 ms vs −2 ms change from baseline, respectively, both $p < 0.001$ vs placebo). QRS interval did not change, but QT interval lengthened (80 and 91 ms for sotalol, each $p < 0.001$ vs +13 ms for placebo, $p < 0.01$). Differences in QT change between placebo and each dose of sotalol were significant ($p < 0.001$). When corrected for heart rate, this differential change was reduced (+22 and +30 ms for sotalol, each $p < 0.01$, and +10 ms for placebo, $p < 0.05$). Although changes for QTc interval, compared with placebo, were not significant, comparisons with JTc interval (QTc corrected for QRS change) were significant ($p = 0.006$ for each dose vs placebo).

Effect on cardiac function: In no patient did clinical heart failure develop as a result of sotalol, and changes in the ejection fraction did not suggest a negative inotropic effect (mean change +3 and +4% after the 2 sotalol doses vs −1% after placebo, difference not significant).

Adverse experience: Summary of adverse experiences during double-blind therapy is presented in Table III. Any adverse experience was frequent during the 6-week study in all 3 groups (43 to 72%) but tended to be higher in the high-dose sotalol group. Those judged to be related to treatment by the blinded investigator occurred in 11, 39 and 51% of patients in the placebo, low- and high-dose sotalol groups, respectively. Adverse effects leading to discontinuation of drug occurred in 0, 1 (3%) and 8 (21%) patients in these 3 groups, respectively. Adverse ventricular arrhythmia, deemed to be "proarrhythmic," were observed in 2 patients taking placebo (1 each with increased VPCs and increased VT events), 1 patient taking low-dose sotalol (increased VPCs only), and 2 taking high-dose sotalol (1 with increased VT events and new sustained VT and 1 with syncope, bradycardia and nonsustained polymorphic VT). Laboratory abnormalities were observed in a small number of patients in each group (5, 2 and 3, respectively) and were not considered treatment-related.

Conclusion: This multicenter comparative study of sotalol and placebo demonstrated that treatment with sotalol, 320 and 640 mg/day, effectively reduced the

TABLE II Efficacy Results: Sotalol Versus Placebo for VPCs

	Percent VPC Reduction			Patient Response Rate*		
Treatment Group (n)	Total VPCs/Hour	Repetitive Ectopy/Hour	VT Events/Day	Total VPCs/Hour	Repetitive Ectopy/Hour	VT Events/Day
Placebo (32)	10	25	41	6	18	32
Sotalol 320 mg/day (32)	75†	80†	91†	34†	52†	61
Sotalol 640 mg/day (78)	88‡	78	82‡	71‡	44	45

* ≥75% reduction in total VPCs/hour or ≥90% reduction in repetitive ectopy/hour or VT events/day.
† $p < 0.05$ vs placebo; ‡ $p < 0.05$ vs placebo and sotalol 320 mg/day.
VPC = ventricular premature complexes; VT = ventricular tachycardia.

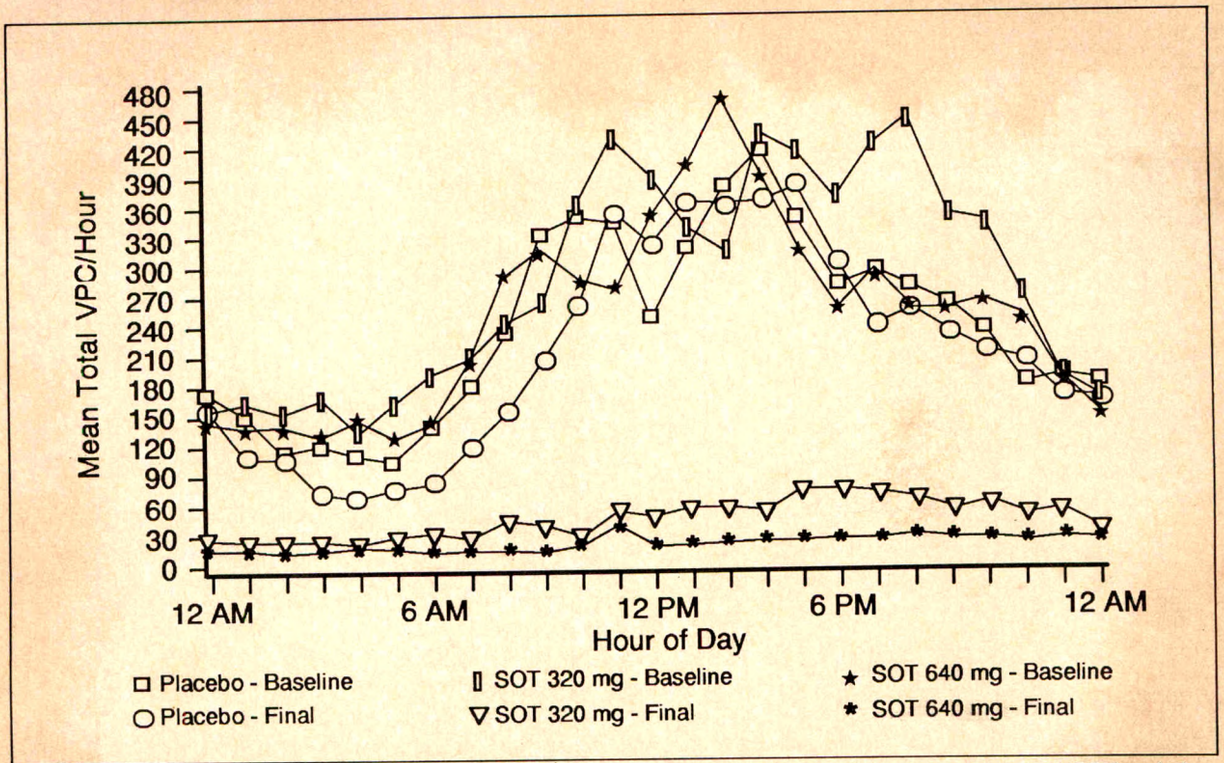


FIGURE 2. Logarithmic mean total ventricular premature complexes (VPCs) per hour, by hour of day, for sotalol (SOT) and placebo groups at baseline and during treatment (6 weeks). Note that sotalol is effective in markedly reducing the total VPCs and in eliminating the circadian rhythmicity of their occurrence.

frequency of total VPCs, repetitive ectopy and VT events in patients with chronic, complex ventricular arrhythmias compared with placebo. Most of the antiarrhythmic efficacy was established early (by day 2 to 3). Repetitive ectopy was more sensitive to suppression by low-dose sotalol than isolated ectopic beats. Effects on the electrocardiogram included reductions in heart rate and modest prolongations of PR and QTc intervals, with a dose-related trend for QTc effect that was not significant. The efficacy of higher dose sotalol was greater than that of lower dose sotalol for reducing isolated VPCs but not repetitive VPC rates. However, the higher dose was somewhat less well tolerated (1 discontinuation because of adverse effects with low-dose sotalol, 8 because of adverse effects with high-dose sotalol). Proarrhythmia was infrequent; it occurred in 3 patients taking sotalol and in 2 taking placebo. One patient also died from a presumed acute myocardial infarction, the onset of which preceded the start of treatment with sotalol, 640 mg 4 times daily. Depression of cardiac function was not observed in the study. Thus, sotalol was efficacious, compared with placebo, with the higher dose being superior to the lower dose in reducing VPC rates, but the higher dose was also somewhat less well tolerated.

TABLE III Adverse Experience Summary: Sotalol Versus Placebo Study

Category (Week 36)	Placebo (n)	Sotalol (320 mg/day) (n)	Sotalol (640 mg/day) (n)
No. of pts	37	38	39
Any OTC (%)	16 (43)	23 (61)	28 (72)
Treatment-related OTC (%)	4 (11)	15 (39)	20 (51)
Discontinued based on OTC (%)	0	1 (3)	8 (21)
Proarrhythmia (VT)	2 (1)	1 (0)	2 (2)*
Lab abnormalities	5 (14)	2 (5)	3 (8)

* 1 = new, sustained VT; 2 = nonsustained, polymorphic VT.
OTC = on treatment condition; VT = ventricular tachycardia.

COMPARATIVE TRIAL OF SOTALOL AND PROCAINAMIDE

The comparative effects of sotalol and a frequently used, standard class I antiarrhythmic agent, procainamide, were assessed in a multicenter Scandinavian trial in patients with chronic ventricular arrhythmias.[9]

Methods: Patients were considered for the study if they had chronic ventricular arrhythmic frequency of ≥60 VPCs/hour, were in stable clinical condition, and met standard inclusion/exclusion criteria similar to those of the sotalol/placebo multicenter study.[7] The study was planned in an open, randomized, crossover design consisting of 4 parts: The first was a single-blind control period during which two 24-hour ambulatory ECG recordings were obtained. The second was an active treatment period for patients with qualifying arrhythmia, after randomization to the first treatment assignment. Sotalol therapy began with an initial dose of 160 mg/day. If VPC reduc-

tion was less than 75% at the end of 1 week, dose was titrated upward to 320, 480 and 640 mg/day, as needed, each at weekly intervals. Procainamide therapy was given as a loading dose of 1.5 g followed by 1 g every 8 hours. After 1 week, a blood level was drawn; if the level was less than 4 μg/ml, the dose was increased to 1.5 g 3 times daily for 1 week. Two 24-hour recordings were obtained at the end of dose titration with the 2 drugs for efficacy determination. The third period consisted of a 1-week washout period (second control phase) ending with a second 24-hour control recording, leading to the fourth part, a second treatment period with the opposite therapy, using the same dose titration sequence.

Thirty-three patients entered the study (average age 55 years, range 30 to 75). They were almost equally divided between men and women (17 vs 16). Twelve had ischemic heart disease, 5 had cardiomyopathy or myocarditis and 3 had hypertension. The mean baseline frequency of VPCs was 18,321/24 hours (range 2,689 to 54,638).

Results: Reduction in VPCs of ≥75% was achieved in 22 patients (67%) with sotalol therapy and in 13 (39%) with procainamide (Table IV). In the sotalol group, all 12 patients with ischemic heart disease were responders, in contrast to only 10 of 21 patients in the procainamide group (100 vs 48%, $p < 0.01$). Six of 12 patients with vs 7 of 21 without ischemic heart disease responded to procainamide (difference not significant). Sixteen patients responded to sotalol with a dose of ≤320 mg/day, and 10 required 480 or 640 mg/day. For the group as a whole, 13 (39%) responded only to sotalol, 4 (12%) only to procainamide, 9 (27%) to both and 7 (21%) to neither drug (Table IV).

Adverse effects, usually fatigue, were noted by 9 patients taking sotalol and prevented completion of the sotalol part of the study in 5 patients. In 1, VT not observed previously was recorded and the patient withdrawn. Adverse effects, most often gastrointestinal, were reported by 12 patients during procainamide therapy. Two of these were unable to complete the study. In 1 patient runs of VT developed for the first time with procainamide, and another had an increase from 2 to 7 episodes of VT.

Conclusion: In this controlled, crossover comparison, the overall effectiveness and tolerance of sotalol appeared as good as or better than that of procainamide, suggesting it to be a useful alternative antiarrhythmic agent for control of chronic VPCs requiring therapy, especially in patients with ischemic heart disease.

TABLE IV Comparative Responses: Sotalol Versus Procainamide (in 33 Patients with Frequent VPCs)*

Successful Regimen	Successful Response (≥75% VPC Suppression) No. (%)
Sotalol, total	22 (67)
Sotalol only	13 (39)
Sotalol/ischemic heart disease	12 (100)
Procainamide, total	
Procainamide only	4 (12)
Procainamide/ischemic heart disease	6 (50)
Both	9 (27)
Neither	7 (21)

* Adapted from *Am Heart J.*[9]

TABLE V Estimated Efficacy and Tolerance of Antiarrhythmic Agents in Patients with Complex VPCs*

Class	Drug	% of Pts. Responding (≥ 75% Suppression)†	% Drug Intolerance
IA	Quinidine	65	30
	Procainamide	60	30
	Disopyramide	60	25
IB	Tocainide	50	40
	Mexiletine	55	40
IC	Flecainide	85	10
	Encainide	80	10
II	Propranolol, etc.	50	15
III	Amiodarone	75‡	10–50§

* The table is provided as an estimate and does not imply direct comparisons among antiarrhythmic agents in patients with complex ventricular arrhythmias.
† Using ambulatory monitoring in patients with baseline VPCs ≥30/hour.
‡ Indicated only for life-threatening ventricular arrhythmias.
§ Dose- and time-dependent; may be life-threatening (pulmonary fibrosis).
VPCs = ventricular premature complexes.

COMPARISON OF SOTALOL WITH QUINIDINE

Quinidine is an important class I antiarrhythmic agent for drug comparison studies, both because of its long and frequent use and because of the large body of comparative data relating its efficacy to that of other antiarrhythmic agents. Quinidine and sotalol have been compared in a multicenter study in patients with complex, chronic ventricular arrhythmias. A comparison of the hemodynamic effects of the 2 agents has already been presented,[10] and the report of their comparative antiarrhythmic effects in 144 patients is in preparation.

Design: The sotalol/quinidine comparative study used a placebo-controlled, multicenter, randomized, double-blind, crossover design.[10] During week 1, washout of other antiarrhythmic agents for at least 4 days (over 5 half-lives) was followed by a screening ambulatory electrocardiogram. Patients with at least 30 VPCs/hour advanced to phase 2. During week 2, a baseline, single-blind, placebo-control period was followed by an ambulatory ECG recording. Patients continuing to show qualifying arrhythmias were randomized to double-blind therapy with either sotalol (320 mg/day) or quinidine (800 mg/day) in divided doses. An ambulatory electrocardiogram was recorded at the end of week 4. For those achieving <75% VPC suppression, compared with baseline, dose was adjusted during weeks 5 and 6 to 640 mg/day for sotalol and 1,600 mg/day for quinidine. The final treatment Holter recording was performed at the end of week 6. A placebo washout (single-blind) occurred during week 7 followed by a second baseline ECG recording before crossover (double-blind) to the alternative therapy, with dose titration and efficacy assessment as for the first treatment phase, during weeks 8 to 11.

Results of hemodynamic comparisons will be summarized in this symposium by Mahmarian et al. Results of the antiarrhythmic efficacy of the 2 agents are being analyzed and are expected to be reported shortly.

COMPARISONS AMONG SOTALOL AND OTHER ANTIARRHYTHMIC AGENTS

Table V presents average antiarrhythmic efficacy for approved agents, based on reported studies.[11,12] In these studies, patients with chronic, frequent ventricular ectopy requiring therapy (similar to the patient groups included in the sotalol studies previously reported on) were treated with various class I, II or III antiarrhythmic agents, and the percentage of patients achieving ≥75% suppression was assessed. In addition, the percentage of patients showing significant adverse effects, preventing adequate drug dosing or requiring drug discontinuation, are given. Response rates average 50 to 55% with class IB agents (tocainide, mexiletine), 60 to 65% with class IA agents (quinidine, procainamide and disopyramide) and 80 to 85% with the new class IC agents (flecainide and encainide). The approximate two-thirds response rates with sotalol, most often in doses of 320 to 640 mg/day, compares favorably with these rates. Rates of discontinuation with class IA and IB agents, averaging 30 to 40%, appear to be higher than has been observed with moderate doses of sotalol. Class IC agents are remarkable for their good tolerance but have the disadvantage of showing significant proarrhythmic potential in patients with reduced ventricular function.[13]

Other factors besides moderate antiarrhythmic effectiveness and relatively low side-effect potential favor the use of sotalol as an antiarrhythmic agent for patients with chronic ventricular arrhythmias, when compared with standard agents. Patients with ventricular arrhythmias may have associated conditions that are beneficially affected by β-blocking therapy, including angina, hypertension and postmyocardial infarction risk status. In addition, treatment of complex ventricular arrhythmias is often undertaken with the hope of reducing excessive risk of sudden cardiac death as well as for symptom reduction. Mortality reductions, including reductions in sudden cardiac death, have been demonstrated to date only for β-blocking drugs,[14–16] including sotalol.[17] Beta blockers are remarkable for their antiarrhythmic and antifibrillatory properties in animal models.[18,19] Little data are available to support the hypothesis that class I antiarrhythmic agents might reduce mortality, and the limited data have not been especially encouraging.[20,21] The National Institutes of Health–supported Cardiac Arrhythmia Pilot Study (CAPS) and Suppression Trial (CAST) are being conducted to resolve this important question.[21,22]

Additional support for the use of sotalol in patients with frequent, complex arrhythmias on ambulatory monitoring is the excellent experience with sotalol, compared with other agents, in the treatment of more malignant, sustained ventricular arrhythmias as assessed by electrophysiologic study.[23–25] The particular benefit of sotalol in suppressing both sustained and nonsustained arrhythmias in patients with ischemic heart disease, those most frequently standing to benefit from therapy, is particularly encouraging.

Conclusion: The antiarrhythmic efficacy of sotalol is well demonstrated by comparisons with placebo, and its effectiveness and tolerance appear likely to be as good as or better than standard (class I) comparison agents. These several considerations support the use of sotalol as a first-line antiarrhythmic agent in many patient groups with complex ventricular arrhythmias requiring therapy for symptom or risk reduction. Results from additional studies and future clinical experience will be of further interest to define these comparisons.

REFERENCES

1. Singh BN, Vaughan Williams EM. A third class of antiarrhythmic action: effects on atrial and ventricular intracellular potentials and other pharmacologic actions on cardiac muscle of MJ 1999 and AH 3676. *Br J Pharmacol 1970;39:675–687.*

2. Singh BN. Control of cardiac arrhythmias by selective lengthening of repolarization: theoretic considerations and clinical observations. *Am Heart J 1985; 109:421–430.*

3. Singh BN, ed. Control of Cardiac Arrhythmias by Lengthening Repolarization. Mt. Kisco, New York: *Futura Publishing, 1988.*

4. Singh BN. Historical development of the concept of controlling cardiac arrhythmias by lengthening repolarization: particular reference to sotalol. *Am J Cardiol 1990;65:3A–11A.*

5. Antonaccio M, Gomoll A. Pharmacology, pharmacodynamics and pharmacokinetics of sotalol. *Am J Cardiol 1990;65:12A–21A.*

6. Deedwania PK. Suppressant effects of conventional beta-blockers and sotalol on complex and repetitive ventricular premature complexes. *Am J Cardiol 1990;65:43A–50A.*

7. Anderson JL, Askins JC, Gilbert EM, Miller RH, Keefe DL, Somberg JC, Freedman RA, Haft LR, Mason JW, Lessem JN. Multicenter trial of sotalol for suppression of frequent, complex ventricular arrhythmias: a double-blind, randomized, placebo-controlled evaluation of two doses. *JACC 1986;8:752–762.*

8. Anderson J, Mason J, Miller RH, Saksena S, Singh S, Somberg J. Sotalol/placebo multicenter comparative study in patients with frequent and repetitive ventricular ectopic activity. Final study report. *Department of Medical Affairs, Bristol-Myers, Company, February 26, 1988.*

9. Lidell C, Rehnqvist N, Sjogren A, Yli-Uotila RJ, Ronnevik PK. Comparative efficacy of oral sotalol and procainamide in patients with chronic ventricular arrhythmias: a multicenter study. *Am Heart J 1985;109:970–975.*

10. Mahmarian JJ, Veroni MS, Holmann T, Hill R, Thornton BC, Bolli R, Young JB, Roberts R, Pratt CM. The hemodynamic effects of sotalol and quinidine: analysis by use of rest and exercise gated radionuclide angiography. *Circulation 1987;76:324–331.*

11. Anderson JL. The new antiarrhythmic agents. How to put them to the best use. *Postgrad Med 1988;83(4):181–193.*

12. Morganroth J, Horowitz LN. Antiarrhythmic drug therapy 1988: for whom, how, and where? *Am J Cardiol 1988;62:461–464.*

13. Morganroth J, Anderson JL, Gentzkow GD. Classification by type of ventricular arrhythmia predicts frequency of adverse cardiac events from flecainide. *JACC 1986;8:607–615.*

14. Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med 1981;304:801–807.*

15. Beta-blocker Heart Attack Study Group. The beta-blocker heart attack trial. *JAMA 1981;246:2073–2074.*

16. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis 1985;27:335–371.*

17. Julian DG, Prescott RJ, Jackson FS, Szekely P. Controlled trial of sotalol for one year after myocardial infarction. *Lancet 1982;1:1142–1147.*

18. Anderson JL, Rodier HE, Green LS. Comparative effects of beta-adrenergic blocking drugs on experimental ventricular fibrillation threshold. *Am J Cardiol 1983;51:1196–1202.*

19. Anderson JL. Antifibrillatory versus antiarrhythmic therapy. *Am J Cardiol 1984;65:7A–13A.*

20. Furberg CD. Effect of antiarrhythmic drugs on mortality after myocardial infarction. *Am J Cardiol 1983;52:32C–36C.*

21. Woosley RW. Indications for antiarrhythmic therapy. A wealth of controversy, a dearth of data. *Ann Intern Med 1988;108:450–451.*

22. The Cardiac Arrhythmia Pilot Study (CAPS) Investigators. Effects of encainide, flecainide, imipramine, and moricizine on ventricular arrhythmias during the year after myocardial infarction: the CAPS. *Am J Cardiol 1988;61:501–509.*

23. Senges J, Lengfelder W, Jauernig R, Czygan E, Brachmann J, Rizos I, Cobbe S, Kübler W. Electrophysiologic testing in assessment of therapy with sotalol for sustained ventricular tachycardia. *Circulation 1984;69:577–584.*

24. Nademanee K, Feld G, Henrickson J, Singh BN. Electrophysiological and antiarrhythmic effects of sotalol in patients with refractory life-threatening ventricular tachyarrhythmias. *Circulation 1985;72:555–564.*

25. Kopelman HA, Woosley RL, Lee JT, Roden DM, Echt S. Electrophysiologic effects of intravenous and oral sotalol for sustained ventricular tachycardia secondary to coronary artery disease. *Am J Cardiol 1988;61:1006–1011.*

Suppressant Effects of Conventional Beta Blockers and Sotalol on Complex and Repetitive Ventricular Premature Complexes

Prakash C. Deedwania, MD

Beta-blocking drugs have been shown to reduce the overall mortality and risk of sudden cardiac death in survivors of acute myocardial infarction. It is not known whether such an effect is mediated by suppression of ventricular premature complexes (VPCs). The circadian rhythmicity of ventricular arrhythmia can also be suppressed by β-blocking drugs, and this may help reduce the risk of sudden cardiac death during the morning hours. Recent studies have also shown that β blockers can provide a safe and effective combination with class IA antiarrhythmic agents when arrhythmias cannot be controlled with class IA agents alone.

Sotalol, a nonselective β antagonist, has unique electrophysiologic properties, and several studies have shown it to be more effective than conventional β blockers in suppressing ventricular arrhythmias. However, direct comparative studies of the suppression of VPCs are lacking. In a recent double-blind, placebo-controlled, parallel study, the antiarrhythmic effects of sotalol and propranolol were compared in 172 patients with >30 VPCs/hour. After the initial 1-week washout and 1-week placebo period, patients were randomly assigned to either 160 mg of sotalol administered twice daily (76 patients) or 40 mg of propranolol administered 3 times daily (91 patients). Those responding to therapy (decreases >75% VPCs) continued to take these doses, but nonresponders were given higher doses, 320 mg of sotalol twice daily or 80 mg of propranolol 3 times daily, respectively. The baseline mean hourly VPC count, derived from two 24-hour Holter recordings during the placebo phase, was 274 for sotalol and 255 for propranolol patients and was reduced to 54 (80% decrease) for sotalol and 104 (59% decrease) for propranolol-treated patients at 6 weeks (p <0.002). A significantly greater percentage of patients (56%) responded to sotalol compared with those who responded to propranolol (29%) (p <0.001). The class III antiarrhythmic activity of sotalol may account for its superiority over propranolol.

(Am J Cardiol 1990;65:43A–50A)

From the Section of Cardiology, Veterans Administration Medical Center, Fresno, and Department of Medicine, University of California San Francisco School of Medicine, San Francisco, California.

Address for reprints: Prakash C. Deedwania, MD, Cardiology Division, Veterans Administration Medical Center, 2615 East Clinton Avenue, Fresno, California 93703.

Although the antiarrhythmic effects of β blockers have been known for more than 2 decades, it is only in the last few years that these agents have gained popularity as antiarrhythmic agents in treating patients with ventricular arrhythmias. Results of several large-scale trials throughout the world clearly demonstrate that β blockers are effective in reducing the risk of sudden cardiac death in survivors of acute myocardial infarction.[1–4] Although the precise mechanism responsible for this reduction in mortality is not clear, it may be due in part to their primary antiarrhythmic action. Beta blockers have been shown to reduce the frequency of spontaneous high-grade ventricular arrhythmias,[5–11] as well as to prevent the induction of ventricular tachycardia (VT) during electrophysiologic studies.[12] However, the latter effect is poorly documented. Beta blockers form the mainstay of therapy in patients with exercise and other forms of catecholamine-induced ventricular arrhythmias.[13,14] Although more than 24 β-blocking agents are now available for clinical or investigational use, sotalol, an investigational compound, has several unique properties[15] that distinguish it in this class of drugs for use as an antiarrhythmic agent in the treatment of ventricular arrhythmias.

Sotalol is a noncardioselective β blocker devoid of membrane-stabilizing or intrinsic sympathomimetic activity and is classified as a class III antiarrhythmic agent by virtue of its ability to prolong cardiac repolarization. This unique combination of class II and class III antiarrhythmic properties caused considerable interest and investigations of its use in managing patients with ventricular arrhythmias.[15,16] Recent reports show that it is an effective antiarrhythmic agent in treating life-threatening and potentially lethal ventricular arrhythmia.[17] The suppressant effect of sotalol on ventricular arrhythmia is particularly interesting because it is not known whether this effect is due solely to its β-blocking action or whether the drug's net suppressant effect in this regard is enhanced by its well-documented propensity to prolong cardiac repolarization.

The primary purpose of this report is to review the available data on the suppressant effects of conventional β blockers and of sotalol on complex and repetitive ventricular premature complexes (VPCs). The effects of sotalol on life-threatening ventricular arrhythmias have been dealt with elsewhere in this symposium. This study compares the effects of sotalol and conventional β-blocking drugs and explores the reasons for superiority of sotalol over conventional β-blocking drugs in controlling ventricular arrhythmias.

PATHOPHYSIOLOGIC CONSIDERATIONS

Before discussing the effects of β-blocking drugs on ventricular arrhythmias, it is important to review the roles of catecholamines and adrenergic stimulation and their relation to circadian variations in ventricular arrhythmias and sudden cardiac death.

Catecholamines and cardiac arrhythmias: It has been known for many years that the sympathetic nervous system plays a significant role in the genesis and perpetuation of potentially serious ventricular tachyarrhythmias.[18] The primary mediators of this neural perpetuation of arrhythmias are adrenergic transmitters. This has been confirmed by experiments demonstrating the prevention of ventricular fibrillation by reserpinization in experimental animals with cardiac glycoside intoxication.[18] It has also been shown that regional cardiac sympathectomy and left stellate ganglionectomy can control recalcitrant ventricular arrhythmias in humans.[18,19]

The electrophysiologic effects of β-adrenergic stimulation on Purkinje fibers and ventricular myocardium are well known and complex. These effects depend primarily on the concentrations of the catecholamines released and on the presence or absence of abnormal cardiac tissue. In normal Purkinje fibers, β-adrenergic stimulation causes no change in the transmembrane potential at rest, the initial portions of the action potential, phase 0 and phase 1, or conduction velocity.[20,21] However, when the Purkinje fibers are paced at a rate sufficient to overdrive spontaneous activity, repolarization is altered with "pure" β-adrenergic stimulation, resulting in modest shortening of the action potential duration. In contrast, α-adrenergic stimulation results in lengthening of the action potential duration.[20,21] The most consistent effect of β-adrenergic stimulation in normal Purkinje fibers is an increased rate of rise of phase 4 depolarizaton, resulting in increased automaticity.

In normal ventricular fibers, the effects of catecholamines on the action potential are quite similar. There is only a minor effect on the resting transmembrane potential, action potential duration and conduction velocity, despite a marked increase in contractile force. The diastolic depolarization is not altered either and, thus, automaticity is not enhanced. However, in the case of partially depolarized fibers, especially after high concentrations of external potassium, catecholamines may markedly augment the upstroke velocity of the resulting slow-response potentials, increasing their amplitude and significantly prolonging their repolarization phases.[21]

Electrophysiologic effects of beta blockade: The electrophysiologic effects of β blockade have been extensively studied in experimental animals and humans[20,21] and will be discussed only briefly. In concentrations that produce substantial β blockade, none of the available β-blocking drugs exerts an effect on the resting transmembrane potential, action potential amplitude, or the maximal rate or rise of the action potential. Thus, these agents do not affect conduction velocity or membrane responsiveness in normal fast sodium-channel-dependent fibers. However, in high concentrations, some of the β blockers (e.g., propranolol, oxprenolol and acebutolol) exert local anesthetic effects on nerves, and they reduce sodium conductance at the cardiac membrane, an effect particularly evident in partially depolarized fibers such as may be found in ischemic myocardium.[21] Under these conditions, β blockers may depress conduction velocity, shift the membrane responsiveness curve in the hyperpolarizing direction and prolong the effective refractory period.[21] The most consistent effect of these drugs is to enhance the rate of rise of spontaneous diastolic depolarization under the influence of catecholamines. The enhanced rate of rise of phase 4 depolarization is depressed by β blockers without significant effect on the threshold potential or the amplitude of the action potential. The overall effect is decreased automaticity in these fibers. Although the effects of β blockers on triggered automaticity are not well established, propranolol has been demonstrated to decrease the amplitude of delayed afterdepolarizations and stop triggering in atrial muscle or Purkinje fibers exposed to high concentrations of catecholamines or cardiac glycosides.[22] This may be one of the main mechanisms by which β-blocking drugs suppress exercise-induced ventricular arrhythmias.[23] Beta-blocking drugs have also been shown to increase ventricular fibrillation threshold under both nonischemic and ischemic conditions.[24] In a recent study of 5 β-blocking drugs in experimental animals, it was clearly demonstrated that all of the β-blocking agents studied produced significant increases in ventricular fibrillation threshold, particularly in the ischemic myocardium (Fig. 1).[24] These findings may help explain the beneficial effect of β blockers in survivors of acute myocardial infarction by protecting against ventricular fibrillation and sudden cardiac death.

Some other unique features of the electrophysiologic actions of β-blocking drugs are the differences between the effects of acute and chronic β blockade on the action potential. It has been shown by Raine and Vaughan Williams[25] that, in animals treated chronically, propranolol and acebutolol produced a modest but significant lengthening of the action potential duration without any effect on the upstroke velocity. It was postulated that these changes during chronic β blockade represent physiologic adaptation. These data have not been confirmed in clinical studies, since studies in humans show that QTc may be shortened, unchanged or prolonged during chronic β-blocking therapy.[21] The overall results from available studies indicate that even if chronic β blockade does prolong the action potential duration, the overall change is minimal with the exception of changes produced by sotalol. As discussed elsewhere in this symposium, sotalol is unique in that it causes significant prolongation of the action potential duration in addition to its β-blocking properties. This property may account for sotalol's superiority in suppressing ventricular arrhythmias.[15]

Catecholamines, beta blockade and circadian variation in arrhythmias: Recent studies have demonstrated a circadian rhythmicity for acute myocardial infarction, transient ischemic events and sudden cardiac death. The increase in sudden cardiac deaths during morning hours may well be due to a significant increase in the frequency of VPCs during the morning hours.[26,27] Twenty-four-

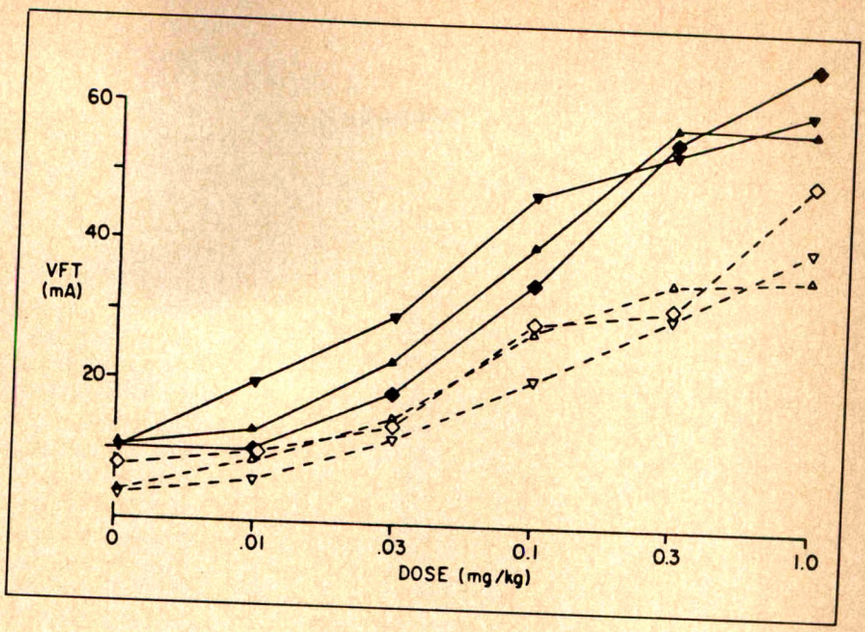


FIGURE 1. Effect on ventricular fibrillation threshold (VFT) of incremental dosing with labetalol (*diamonds*), metoprolol (*wedges*) and propranolol (*triangles*). The VFT in milliamperes is shown on the *vertical axis* and the drug dose on the *horizonatal axis*. Measurements during ischemia are represented by *open symbols* connected by *dashed lines*. Those with ischemia are represented by *solid symbols* and *lines*. (Reproduced with permission from *Am J Cardiol.*[24])

hour Holter monitorings in patients with ventricular arrhythmia show that the frequency of VPCs increases in the morning hours. It has been postulated that this morning increase in ventricular arrhythmia density, in conjunction with the increases observed in transient myocardial ischemic events and acute myocardial infarctions, may account for the increased risk of sudden cardiac deaths in the morning hours. Although the precise mechanism of circadian rhythmicity of ventricular arrhythmias and ischemic events is not established, it is possible that the morning surges in catecholamines may be responsible for the genesis of these conditions and explain the effects of β-adrenoceptor blockade in their control. Recent studies demonstrate that β blockade with acebutolol (Fig. 2) or nadolol attenuate or abolish the circadian rhythmicity of VPCs.[26,27] This decrease in the density of ventricular arrhythmias during morning hours by β blockade may be responsible for the beneficial effects of these agents in reducing sudden cardiac deaths by removing this trigger for ventricular fibrillation in the setting of coronary artery disease.

SUPPRESSANT EFFECTS OF CONVENTIONAL BETA BLOCKERS ON VENTRICULAR PREMATURE COMPLEXES

Recent studies[5,6,26–30] using a variety of conventional β-blocking agents have evaluated the suppressant effects of these agents on VPCs, including complex and repetitive ventricular ectopy (Table I). The results from most of these studies demonstrate nearly 50% efficacy of conventional β-blocking drugs in suppressing VPC frequency, and 40 to 50% of the patients achieve ≥75% VPC sup-

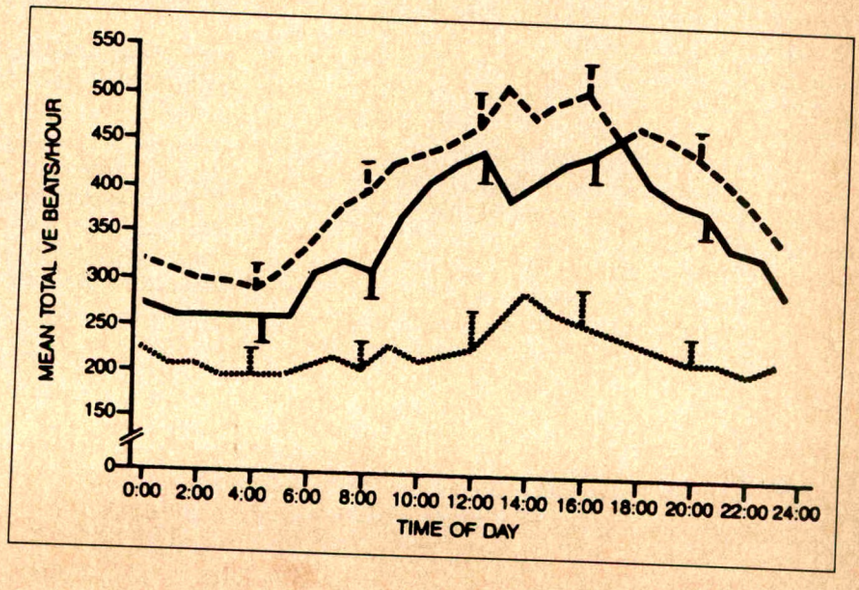


FIGURE 2. Circadian variation of mean total ventricular premature complexes/hour (mean ± standard error of the mean) at baseline (*broken line, top*), during placebo administration (*solid line, middle*) and with acebutolol (*dotted line, bottom*). Acebutolol markedly attenuated circadian distribution of ventricular premature complexes. VE = ventricular ectopic. (Reproduced with permission from *Am Heart J.*[26])

TABLE I Antiarrhythmic Effects of Conventional Beta Blockers in Benign or Potentially Lethal Ventricular Arrhythmias Relative to Those of Sotalol

Study and Reference	Drug Dose Used	Maximal VPCs/hour (mg/day)	% Reduction	Patients with Efficacy (%)
Woosley[5]	Propranolol	960	70–100	24/32 (75)
Singh[28]	Acebutolol	1,800	52	—
	Propranolol	240	47	—
Pratt[29]	Metoprolol	200	60	10/20 (50)
Chandraratna[26]	Acebutolol	1,800	74	14/42 (33)
	Propranolol	240	60	9/42 (20)
Nademanee[6]	Nadolol	640	86	17/36 (48)
Morganroth[30]	Nadolol	160	85	11/23 (48)
Myburgh[32]	Sotalol	160	86	—
Mary-Rabine[33]	Sotalol	160	—	5/10 (50)
Myburg[37]	Sotalol	320	58	10/22 (45)
	Nadolol	160	61	7/22 (32)
Anderson[16]	Sotalol	640	83	33/56 (59)
Deedwania[38]	Sotalol	640	80	35/63 (56)
	Propranolol	240	59	22/77 (29)

VPCs = ventricular premature complexes.

pression. However, it is difficult to compare the results of these studies because the selection criteria for patients studied, duration of treatment, as well as doses of β-blocking drugs used, varied considerably.

In the study by Woosley et al,[5] 32 patients with stable and frequent ventricular tachyarrhythmias received propranolol given in incremental doses until a defined degree of arrhythmia suppression was achieved, adverse effects developed, or the maximal dose of 960 mg/day was reached. These investigators demonstrated a 70 to 100% suppression of ventricular arrhythmia with adequate response achieved in 75% of the patients. Eight patients had episodes of VT that responded to lower doses of propranolol than those required to suppress VPCs.

More recently, Nademanee et al[6] reported that, during nadolol treatment with doses titrated up to 640 mg/day, 48% of the 36 patients studied achieved ≥75% suppression of ventricular ectopy. Similar to the results of Woosley et al, these investigators also found that nadolol was effective in reducing VT events by 75% in all of the 13 patients who had these arrhythmias at baseline. This dramatic effect of nadolol on VT events is unusual and has not been observed in other β-blocking trials, and may be due to higher than usual doses of nadolol used. In another study, Morganroth and Duchin[30] evaluated the antiarrhythmic effects of low-dose nadolol in 23 patients with benign or potentially lethal ventricular arrhythmias. Forty-eight percent of patients responded to nadolol with a reduction of >75% in arrhythmia frequency, and several patients responded taking as low as 10 mg/day of nadolol.

The antiarrhythmic efficacy of acebutolol and propranolol was evaluated in a double-blind, placebo-controlled, randomized, crossover study by Singh et al.[28] In this study of 31 patients with more than 30 VPCs/hour, both acebutolol and propranolol produced comparable (52 and 47%, respectively) and significant reductions in VPC frequency during both 24-hour Holter monitoring evaluation and exercise testing (51 and 69%, respectively).

In a recent report summarizing the results of 3 large multicenter clinical trials, Chandraratna[26] reported the comparative efficacy of acebutolol, placebo, propranolol and quinidine in a total of 217 patients with chronic frequent VPCs. As shown in Table II and III, acebutolol significantly ($p < 0.002$ to $p < 0.001$) reduced mean total VPCs as well as complex VPCs compared with baseline. The efficacy of acebutolol was superior to placebo and comparable to that of propranolol and quinidine. Also, the number of patients with adequate (≥75%) suppression of VPCs was comparable for acebutolol, propranolol and quinidine.

The results from studies just discussed indicate that most conventional β-blocking drugs significantly suppress VPCs in patients both with and without organic heart disease. These effects are characterized by (1) a significant reduction in VPC frequency with adequate (≥75%) suppression in approximately 50% of the patients, (2) a greater response for higher grades (complex VPCs and ventricular couplets) of VPCs, and (3) abolition or marked attenuation of the circadian pattern of VPC distribution (Fig. 2). Another major advantage of β blockers in comparison with other antiarrhythmic drugs has been a relatively good safety record with very few adverse effects.

In general, β blockers have not been shown to produce proarrhythmic effects. Because of their good safety record and different mechanism of action, β blockers also are frequently used in combination therapy with class I antiarrhythmic agents. In a recent study,[31] the effects of β blockade with nadolol combined with procainamide and quinidine were studied in 18 patients refractory to class IA agents alone. The combination therapy significantly reduced total VPC frequency during titration as well as during the double-blind phase (Fig. 3). A positive response, defined as a decrease of ≥75% in VPCs, was documented in 57% of patients during the titration phase and 63% of patients during double-blind treatment.

SOTALOL AND SUPPRESSION OF VENTRICULAR PREMATURE COMPLEXES

Because of its unique electrophysiologic spectrum of action, sotalol is thought to be superior to conventional β-blocking agents in treating ventricular arrhythmias. However, as discussed, most conventional β blockers have also been shown to suppress ventricular arrhythmias; thus, to demonstrate its superiority, it is essential to compare the relative potency of sotalol to that of conventional β-blocking agents.

The antiarrhythmic efficacy of sotalol on VPCs has been known for many years. Earlier studies were performed in small numbers of patients using inadequate dosages of sotalol. Recently, in the study by Myburgh et al,[32] optimally titrated doses of sotalol suppressed the frequency of VPCs by 86% in 20 patients with ischemic heart disease. Mary-Rabine et al[33] reported the long-term effects of sotalol in doses of 80 to 160 mg/day in 10

TABLE II Summary of Efficacy Results: Acebutolol Versus Propranolol in Ventricular Arrhythmia (n = 42)

Parameters	Baseline	Acebutolol		Propranolol		
		Dose Titration	Maintenance	Dose Titration	Maintenance	Drug Free
Mean total VPCs/hour	26.5 ± 44.5	63.6 ± 17.2	82.3 ± 22.3	115.3 ± 31.1	140.3 ± 40.3	222.6 ± 41.0
Minimum VPCs/hour	33.8 ± 9.1	8.1 ± 2.5	11.6 ± 3.6	20.1 ± 6.2	27.8 ± 9.2	36.4 ± 10.8
Maximum VPCs/hour	677.5 ± 93.8	299.1 ± 61.9	299.0 ± 65.9	410.3 ± 84.6	375.0 ± 82.0	629.3 ± 80.5
Mean paired VPCs/hour	15.6 ± 4.6	4.3 ± 1.3	5.3 ± 2.7	6.3 ± 2.1	8.8 ± 3.6	8.5 ± 2.6
Mean VT beats/hour	1.0 ± 0.3	0.3 ± 0.2	0.1 ± 0.0	0.3 ± 0.1	0.2 ± 0.1	1.3 ± 0.6
Multiform beats (%)*	63.3 ± 6.2	49.4 ± 6.1	56.3 ± 6.0	60.5 ± 6.2	61.4 ± 5.9	66.0 ± 6.2
R-on-T beats (%)	1.7 ± 0.9	1.2 ± 1.2	0.4 ± 0.3	0.1 ± 0.1	0.2 ± 0.1	0.1 ± 0.1
% Below baseline minimal total VPCs†	0.0 ± 0.0	73.8 ± 6.9	73.8 ± 6.9	54.8 ± 7.8	59.5 ± 7.8	38.1 ± 7.6
Mean hourly heart rate	73.3 ± 1.4	64.1 ± 1.1	66.7 ± 1.2	63.6 ± 1.2	63.6 ± 1.2	78.6 ± 1.7

* Hours noted.
† Twenty-five percent of observations are generally expected to be less than the minimum of 3 preceding observations.
Values are mean ± standard error of the mean.
VPC = ventricular premature complexes; VT = ventricular tachycardia.
Adapted with permission from *Am Heart J.*[26]

patients with organic heart disease and symptomatic ventricular ectopy. Serial Holter recordings were obtained before sotalol was started and then at 3- and 6-month intervals during sotalol therapy. Initially, a significant suppression of ventricular ectopy was observed in 9 of 10 patients and, during long-term therapy, the efficacy was maintained in 50% of the patients, including suppression of complex and repetitive ectopy.

In a more recent double-blind, placebo-controlled study, Anderson et al[16] evaluated the suppressant effects of sotalol, given in doses of 320 or 640 mg/day, on complex ventricular ectopy in 56 patients with chronic VPCs. The doses significantly reduced the median arrhythmia frequency by 77 and 83%, respectively ($p < 0.001$), compared with a 6% reduction during placebo administration. Fifty-nine percent of the sotalol group achieved adequate suppression, defined as 75% reduction in ventricular ectopy, compared with an 11% response in the placebo group. The effects of sotalol on couplets and runs of nonsustained VT were even more dramatic, showing a 94% ($p < 0.0001$) and 89% ($p < 0.0007$) reduction, respectively.

Another blinded, placebo-controlled study[34] demonstrated the efficacy of sotalol in suppressing VPCs. Fourteen patients with history of myocardial infarction and high-density, stable VPCs were given 320 mg of sotalol or matching placebo. In 6 of 14 patients, the total number of VPCs decreased by 50% with greater suppression of the higher grades of ventricular ectopy. There were no adverse reactions and left ventricular ejection fraction was unchanged. In addition, a significant ($p < 0.0005$) correlation was noted between an antiarrhythmic effect and the prolongation of the QTc interval.

Wang et al[35] examined the significance of the lengthening of cardiac repolarization on heart rate and arrhythmia suppression induced by sotalol. Seventeen patients followed an incremental dose-regimen protocol under serum drug-concentration control. Sotalol at doses of 160, 320, 640 and 960 mg was given once or twice daily. Eleven of the 17 patients derived antiarrhythmic response with a 70 to 100% reduction of VPCs at a wide range of plasma concentrations; the responders included 8 patients who had poor responses with conventional β-blocking therapy. The sotalol concentration at which QTc prolongation was noted (2.55 mg/liter) was greater than that producing 50% reduction in exercise-induced increases in heart rate (0.80 mg/liter).

The antiarrhythmic effects of sotalol have also been

TABLE III Summary of Efficacy Results: Acebutolol Versus Quinidine in Ventricular Arrhythmia

	Baseline*	Acebutolol*	Quinidine*	Drug Free
Heart rate (beats/min)				
Resting	83.1 ± 2.7	65.0 ± 1.7	82.4 ± 2.9	81.1 ± 3.1
Peak	110.9 ± 4.0	93.3 ± 2.9	111.6 ± 3.7	111.3 ± 3.7
VPCs (rate/hour)				
At rest (Holter)	223.6 ± 48.4	97.8 ± 37.5	137.5 ± 49.3	145.1 ± 42.7
During exercise†	501 ± 73.8	158.4 ± 52.2	262.2 ± 75	305.4 ± 70.2
Higher grade VPCs				
At rest (VPCs/hour)	2.43 ± 0.55	1.14 ± 0.47	0.87 ± 0.21	1.96 ± 0.65

* Based on average of two visits.
† Computed as rate/hour.
Values are mean ± standard error of the mean.
Adapted with permission from *Am Heart J.*[26]

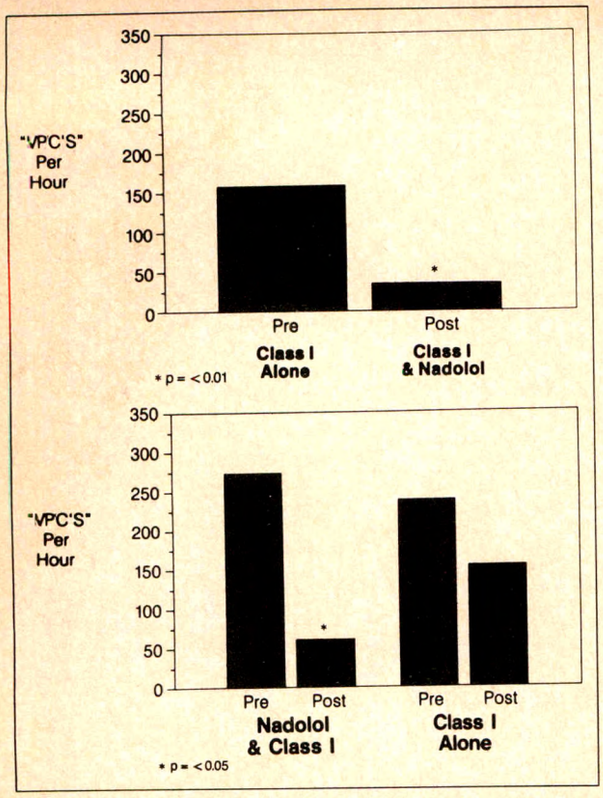


FIGURE 3. ***Top,*** **mean hourly ventricular premature complex (VPC) frequency at baseline and at the end of nadolol dose titration.** ***Bottom,*** **mean hourly VPC frequency before and after double-blind therapy with nadolol plus a class I agent or a class I agent alone. (Adapted from** ***Am J Cardiol.***[31]**)**

compared with those of class I antiarrhythmic agents. In a recent study, Lidell et al[36] compared the efficacy of oral sotalol (160 to 640 mg/day) and procainamide (1 to 1.5 g 3 times daily) in 33 patients with chronic, stable VPCs in an open, randomized, crossover study. Sotalol produced >75% reduction of VPCs in 67% of the patients. Procainamide was effective in 39%. When VPCs were significantly reduced, both drugs induced comparable reductions in runs of nonsustained VT. Nine patients responded to both agents, and 7 failed to respond to either of the drugs.

The results of these studies indicate that sotalol is an effective antiarrhythmic agent and causes significant reductions in the total VPC frequency as well as complex and repetitive ventricular ectopy. The overall response rates achieved during treatment with sotalol in these studies appear to be better than those reported with conventional β blockers in treating patients with chronic ventricular arrhythmia.

COMPARATIVE EFFECTS OF SOTALOL AND CONVENTIONAL BETA BLOCKERS IN SUPPRESSION OF VENTRICULAR PREMATURE COMPLEXES

Whether sotalol is more effective than conventional β blockers can be established only by direct comparison of equiactive β-blocking doses of sotalol and conventional β-blocking drugs in a stable population of patients with comparable ventricular arrhythmias. Little data are available for such direct comparison.

In a single-blind, crossover trial, Myburgh et al[37] compared the suppressant effects of sotalol and nadolol on ventricular ectopy in 22 patients with stable chronic ventricular arrhythmias. All patients had ≥1 acute myocardial infarction at least 3 months before the study and were required to have ≥30 VPCs/hour during the 24-hour Holter monitoring at baseline after withdrawal of all antiarrhythmic agents including β-blocking agents. After a 2-week placebo period, patients began therapy with either 160 mg of sotalol or 80 mg of nadolol once daily in a randomized fashion. After 1 week of active therapy, patients were evaluated, and the dosage of the study drug was doubled in those not achieving a 90% reduction in VPC frequency. Patients were reevaluated after another week of therapy with the effective or highest dosage. This was followed by another 7-day placebo period before crossing over to the other drug, and the sequence of events was repeated exactly as before.

At baseline, the average hourly VPC count was 238 and decreased to 146 (61% reduction) during therapy with 80 mg of nadolol. Seventeen patients were advanced to the higher dose of nadolol (160 mg) because of an inadequate response, and only 2 of the 17 achieved 90% suppression at the higher dose. These data revealed that a higher dose of nadolol was no more effective than the lower dose. In contrast, during sotalol treatment, the baseline average hourly VPC count was 256 and decreased to 199/hour during low-dose administration with a further reduction to 109/hour during high-dose administration. The higher dosage of sotalol was significantly ($p < 0.02$) more effective than the lower dose. Using ≥90% suppression as the criterion for adequate suppression, only 7 patients achieved the desired response, but 10 patients (45%) showed ≥75% VPC suppression during sotalol treatment. Because the highest dose of sotalol was only 320 mg, a higher dosage of sotalol may have produced greater VPC suppression. This is partially supported by the fact that the average heart rate over 24 hours decreased to only 67 and 65 beats/min (from a baseline heart rate of 85 beats/min) during 160 and 320 mg/day of sotalol compared with 64 and 63 beats/min during 80 and 160 mg/day of nadolol. The QTc interval was not prolonged in these patients during sotalol therapy, further suggesting the possibility of inadequate dosage and the potential for additional benefit from higher doses producing prolongation of the QTc interval.

In a more recent double-blind, placebo-controlled, parallel study, Deedwania et al[38] compared the effects of sotalol and propranolol in 172 patients with chronic stable frequent (average of >30 VPCs/hour) ventricular arrhythmias that would generally warrant treatment in clinical practice. Seventy-three percent of the patients were men (mean age 62 years). All antiarrhythmic drugs and β-blocking agents were discontinued during the initial week and placebo was administered for 7 additional days. Two 24-hour Holter recordings were obtained at the end of the placebo phase, and qualifying patients with an average of ≥30 VPCs/hour were randomized to 160

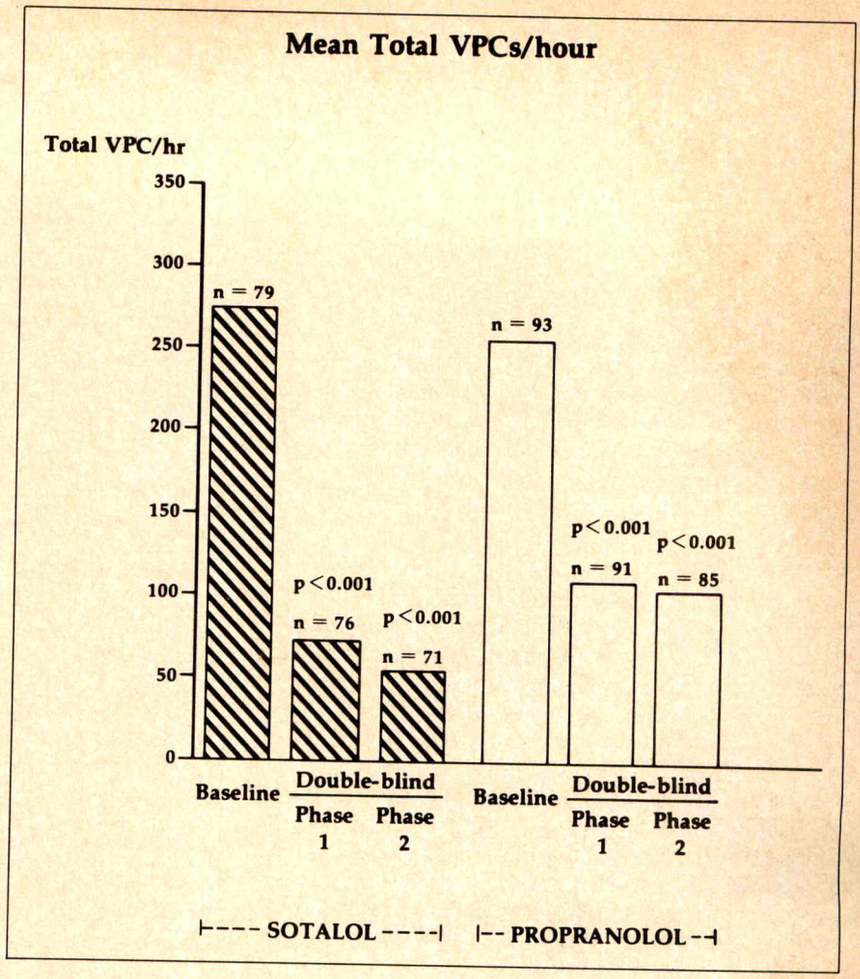


FIGURE 4. Effects of sotalol and propranolol on mean total hourly ventricular premature complex (VPC) frequency during initial (phase 1) and final (phase 2) 2 weeks of double-blind treatment. (Adapted from *Circulation*.[38])

mg of sotalol twice a day (76 patients) or 40 mg of propranolol 3 times a day (91 patients). Adequate VPC suppression was defined as ≥75% reduction in frequency, and patients not achieving this response during the initial 2-week therapy were advanced to higher doses consisting of 320 mg of sotalol twice daily or 80 mg of propranolol 3 times a day. The treatment was then continued for another 2 weeks, and 24-hour Holter recordings were obtained at the end of this treatment. In the group receiving sotalol, the mean hourly VPC count on two 24-hour Holter recordings was 274 and decreased to 54 (80% reduction) by the end of 4 weeks of therapy (Fig. 4). In contrast, in the propranolol-treated group, the baseline mean hourly VPC count was 255 and decreased to 104 (59% reduction) by the end of 4 weeks of propranolol therapy. Fifty-six percent of patients treated with sotalol achieved adequate suppression (≥75% reduction) of VPCs compared with only 29% of the patients receiving propranolol.

DISCUSSION

This review of currently available data indicates that sotalol and conventional β-blocking agents are effective in suppressing VPCs in patients with and without heart disease. The results of 2 comparative studies with sotalol and conventional β-blocking agents, nadolol and propranolol, indicate that sotalol is more effective than both conventional β blockers in suppressing total VPC frequency as well as complex and repetitive ectopy. Although more studies directly comparing sotalol and conventional β blockers are needed, the preliminary results from our study of 172 patients with potentially lethal ventricular arrhythmias show significant superiority of sotalol over propranolol in reducing the frequency of chronic stable VPCs. Furthermore, the percentage of patients achieving adequate (≥75%) suppression of VPCs was significantly greater (56%) with sotalol than with propranolol (29%). Data presented elsewhere in this symposium by Nademanee and Singh[39] also indicate sotalol's usefulness in patients with symptomatic sustained VT or ventricular fibrillation, even when these arrhythmias were refractory to available conventional antiarrhythmic agents. In these patients, sotalol was found to be a powerful suppressant, having selectivity of action, as in the case of most β blockers, for the complex and repetitive forms of VPCs.

Although the data appear to be reasonably compelling, that sotalol might exert a more powerful suppressant effect on VPCs than conventional β blockers, the precise reason for the difference is not clear. Two possibilities should be considered. First, the difference may relate solely to differences in the extent of β-blocking potencies of the doses of the drugs used chronically. To achieve

quantitatively equivalent β-blocking effects by any 2 β antagonists is notoriously difficult. Sotalol has 100% bioavailability and a rapid onset of action and prolonged duration of activity due to a long elimination half-life. These properties may permit more pronounced and continuous β blockade than many other β blockers, with a consequent effect on arrhythmia suppression. The other possibility that has been suggested[35] is that the associated class III action of sotalol might contribute to its overall effect of suppressing VPCs. However, Singh[40] indicated that the "isolated" lengthening of the action potential duration (a class III effect) does not necessarily constitute a powerful mechanism for VPC suppression. For example, clofilium, an adrenergic neuron-blocking drug, produces a massive lengthening of cardiac repolarization but is devoid of a suppressant effect on VPCs.[40] A synergistic effect between β blockade and prolonged cardiac repolarization cannot be excluded.

CONCLUSION

Whatever mechanism might be established for the apparently greater suppressant effect of sotalol on VPCs relative to conventional β blockers, the clinical implications of the observation should be emphasized. There are 2 consequences of the suppressant effect on VPCs and the pronounced and predictable effect on the effective refractory period of cardiac muscle. First, removal of the trigger mechanism by the antiectopic action will reduce the probability of the arrhythmias being initiated. Second, lengthening the refractory period will be associated with an antifibrillatory mechanism resulting from the widening of the tachycardia cycle length. These electrophysiologic mechanisms of sotalol, in conjunction with its known anti-ischemic actions, are likely to provide the basis for reducing the incidence of sudden death from arrhythmias in patients with coronary artery disease.

REFERENCES

1. Wilhelmsen C, Wilhelmsen L, Vedin JA. Reduction of sudden death after myocardial infarction by treatment with alprenolol. *Lancet 1974;2:1157–1161.*

2. Beta Blocker Heart Attack Study Group. The Beta Blocker Heart Attack Trial. *JAMA 1981;246:2073–2080.*

3. The Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med 1981;304:802–809.*

4. The MIAMI Trial Research Group. Mortality. *Am J Cardiol 1985;56:15D–20D.*

5. Woosley RL, Kornhauser D, Smith R, Rede S, Higgins SB, Nres AS, Shand DG, Oates JA. Suppression of chronic ventricular arrhythmias with propranolol. *Circulation 1979;60:819–824.*

6. Nademanee K, Schleman MM, Singh BN, Morganroth J, Reid PR, Stritar JA. Beta-adrenergic blockade by nadolol in control of ventricular arrhythmias. *Am Heart J 1984;208:1109–1116.*

7. Coumel P, Esoubet B, Attuel P. Beta-blocking therapy in atrial and ventricular tachyarrhythmia: experience with nadolol. *Am Heart J 1984;108:1098–1102.*

8. Aronow WS, Turbow M, Lurie M, Whittaker K, Van Camp S. Treatment of premature ventricular complexes wth acebutolol. *Am J Cardiol 1979;43:106–110.*

9. Gradman AH, Winkle RA, Fitzgerald JW, Meffin PJ, Stoner J, Bell PA, Hanson DC. Suppression of premature ventricular contractions by acebutolol. *Circulation 1977;55:785–789.*

10. Podrid PJ, Lown B. Pindolol for ventricular arrhythmias. *Am Heart J 1982;104:491–495.*

11. Morganroth J. Short-term evaluation of atenolol in hospitalized patients with chronic ventricular arrhythmias. *Drugs 1983;25 suppl 2:181–186.*

12. Mason JW, Winkle RA. Accuracy of the ventricular induction study for predicting long-term efficacy and inefficacy of antiarrhythmic drugs. *N Engl J Med 1980;303:1073–1079.*

13. Wu D, Kou KC, Hung JS. Exercise-triggered paroxysmal ventricular tachycardia. *Ann Intern Med 1981;95:410–414.*

14. Palileo EV, Ashley WW, Swiryn S, Bauernfeid RA, Strasberg B, Petropoulos AT, Rosen KM. Exercise provocable right ventricular outflow tract tachycardia. *Am Heart J 1982;104:185–193.*

15. Singh BN, Deedwania P, Nademanee K, Ward A, Sorkin EM. Sotalol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use. *Drugs 1987;34:311–349.*

16. Anderson JL, Askings JC, Gilbert EM, Miller RH, Keefe DL. Multicenter trial of sotalol for suppression of frequent, complex ventricular arrhythmias: a double-blind, randomized placebo-controlled evaluation of two doses. *JACC 1986;8:752–762.*

17. Nademanee K, Feld G, Hendrickson JA, Singh PN, Singh BN. Electrophysiologic and antiarrhythmic effects of sotalol in patients with life threatening ventricular tachyarrhythmias. *Circulation 1985;72:555–564.*

18. Singh BN, Jewitt DE. Adrenoceptor blocking drugs in cardiac arrhythmias. *Drugs 1974;7:426–461.*

19. Ebert PA, Allgood RJ, Sabiston DC. The antiarrhythmic effects of cardiac denervation. *Ann Surg 1968;168:728–735.*

20. Venditti FJ, Garan H, Ruskin JN. Electrophysiologic effects of beta-blockers in ventricular arrhythmias. *Am J Cardiol 1987;60:3D–9D.*

21. Singh BN, Nademanee K. Antihypertensive compounds as antiarrhythmic agents: focus on beta-blocking drugs in ventricular arrhythmias. *Am Heart J 1987;114:1040–1050.*

22. Hewett K, Rosen MR. Beta-adrenergic modulation of the digitalis-induced delayed afterdepolarization and triggered activity (abstr). *Am J Cardiol 1982; 49:913.*

23. Sung RJ, Tai DY, Svinarich JT. Beta-adrenoceptor blockade: electrophysiology and antiarrhythmic mechanisms. *Am Heart J 1984;108:1115–1120.*

24. Anderson JL, Rodier HE, Green LS. Comparative effects of beta-adrenergic blocking drugs on experimental ventricular fibrillation threshold. *Am J Cardiol 1983;51:1196–1202.*

25. Raine AEG, Vaughan Williams EM. Adaptation to prolonged beta-blockade on rabbit atrial, Purkinje and ventricular potentials and papillary muscle contractions. *Circ Res 1981;48:804–812.*

26. Chandraratna PAN. Comparison of acebutolol with propranolol, quinidine, and placebo: results of three multicenter arrhythmia trials. *Am Heart J 1985;109:1198–1204.*

27. Mir MA, Tirlapur VG. Circadian rhythm of ventricular arrhythmias and antiarrhythmic efficacy of long-acting beta-adrenergic blocker. In: Hollenberg NK, ed. The Hemodynamics of Nadolol. Second International Symposium Royal Society of Medicine Series No. 51. *New York: Academic Press, and Grune & Stratton, 1982;101–107.*

28. Singh SN, DiBianco R, Davidov ME, Gottdiener JS, Johnson WL, Laddu AR, Fletcher RD. Comparison of acebutolol and propranolol for treatment of chronic ventricular arrhythmia: a placebo-controlled, double-blind, randomized crossover study. Circulation 1982;65:1356–1364.

29. Pratt CM, Yepsen SC, Kimbloom MG, Taylor AA, Young JB, Quinones MA. Evaluation of metoprolol in suppressing complex ventricular arrhythmias. *Am J Cardiol 1983;52:73–78.*

30. Morganroth J, Duchin KL. Antiarrhythmic effects of beta-adrenergic blocking agents in benign or potentially lethal ventricular arrhythmias. *Am J Cardiol 1987;60:10D–14D.*

31. Deedwania P, Olukotun AY, Kuppersmith J, Jenkins P, Golden P. Beta-blockers in combination with class I antiarrhythmic agents. *Am J Cardiol 1987;60:21D–26D.*

32. Myburgh DP, Goldman AP, Cartoon J, Schamroth JM. The efficacy of sotalol in suppressing ventricular ectopic beats. *Afr Med J 1979;56:295–298.*

33. Mary-Rabine L, Soumagne D, Stiels B. Long-term sotalol therapy in patients with ventricular arrhythmias. *Acta Cardiol 1986;2:89–97.*

34. Burchkardt D, Pfisterer M, Hoffman A, Burkart F, Emmenegger H. Effects of the beta-adrenoceptor blocking agent sotalol on ventricular arrhythmias in patients with chronic ischemic heart disease. *Cardiology 1983;70:suppl 1:114–121.*

35. Wang T, Bergstrand RH, Thompson KA, Siddoway LA, Duff HJ. Concentration-dependent pharmacologic properties of sotalol. *Am J Cardiol 1986; 57:1160–1165.*

36. Lidell C, Rehnqvist N, Sjogren A, Yli-Uotila RJ, Ronnevik PK. Comparative efficacy of oral sotalol and procainamide in patients with chronic ventricular arrhythmias: a multicenter study. *Am Heart J 1985;109:970–975.*

37. Myburgh DP, Smith R, Diamond TH, Faitelson HL, Sommers DK. A comparison of the efficacy of sotalol and nadolol in the suppression of ventricular ectopic beats. *S Afr Med J 1983;63:263–265.*

38. Deedwania P, Morganroth J, Sotalol Study Group. Sotalol is more effective than propranolol in the treatment of potentially lethal ventricular arrhythmia (abst). *Circulation 1988;78:suppl III:III–626.*

39. Nademanee K, Singh BN. Effects of sotalol on ventricular tachycardia and fibrillation produced by programmed electrical stimulation: comparison with other antiarrhythmic agents. *Am J Cardiol 1990;65:53A–57A.*

40. Singh BN. Editorial: When is it QT prolongation antiarrhythmic and when is it proarrhythmic? *Am J Cardiol 1989;63:867–869.*

Discussion II: Sotalol and Suppression of Ventricular Premature Complexes

Dr. Jeffrey Kluger (Farmington, Connecticut): Dr. Anderson, I was interested in your data on the ventricular premature complex (VPC) suppressant effects of sotalol. Have you analyzed your data on the magnitude of suppression relative to heart rate changes?

Dr. Jeffrey Anderson (Salt Lake City, Utah): I do not recall a specific analysis on that point. It is, however, an interesting and important question. What might you expect?

Dr. Kluger: I think that reducing the heart rate will reduce the VPC frequency, and the question arises whether sotalol then acts as a β blocker or additionally as a class III antiarrhythmic.

Dr. Anderson: I think that Dr. Deedwania's data support the latter possibility. It shows suppressant action on the circadian rhythmicity of VPC occurrence; the spontaneous frequency in the group was greater during daytime hours. Presumably, if the heart rate had been plotted against the VPC frequency, there might have been evidence of parallelism between the effects. One might have expected a greater VPC reduction induced by sotalol when the heart rate was higher under baseline conditions. I wonder if it would be more appropriate to look at VPC frequency as a function of heart rate, as Dr. Lawrence Hinkle did in the 1970s using VPC counts per thousand beats as a way of evaluating the VPC frequency.

Dr. Bramah Singh (Los Angeles, California): Perhaps; however, the clinical significance of such an approach is not immediately apparent.

Dr. Steven Singh (Washington, D.C.): Could you give us the incidence of the proarrhythmia as seen in these patients in your outpatient studies?

Dr. Anderson: In the placebo-controlled study that I presented, there were 2 instances requiring stopping the drug from the high-dose group because of a "proarrhythmia." In 1, there was new sustained ventricular tachycardia (VT). In the other, there was syncope, bradycardia and some salvos; what this was caused by was not clear. There was only 1 death in the study and that was in 1 patient (among 114) who sustained a new myocardial infarction. His chest pain began before he took the first dose of sotalol.

Dr. Steven Singh: The incidence of proarrhythmia can be looked at in several ways. One is clearly the development of life-threatening events; another is an increase in VPCs. In the case of encainide and flecainide, at least in the CAPS study, the proarrhythmia was 2 to 4% as seen by Holter monitoring during the initial hospital stay. Do you judge the incidence the same way as for outpatients? Would you still expect the incidence to be 2 to 4%?

Dr. Anderson: Yes, it was in that range for sotalol. Roughly 1 or 2 of 65 in the 2 groups would be in that range, 2 to 4%. Of course, the precise percentage will depend on how you define a proarrhythmia, and this should be standardized.

Dr. James Reiffel (New York, New York): Sotalol is being compared with several other agents such as those from classes IA, IB and IC in the Holter vs the Electrophysiologic Programmed Studies trial in patients with lethal ventricular arrhythmias. Although the results of this study will not be known until 1992 or 1993, I can comment based on results at our own center. The results for sotalol are quite favorable, if not better than those for the alternative agents in that trial. The Safety Board has found no increased incidence of proarrhythmic events in the sotalol population or the drug would have been removed from the trial.

Dr. Bramah Singh: That is interesting and important. I have believed for a long time that drugs that prolong refractoriness without much effect on conduction are likely to be more effective and less proarrhythmic. Your data are consistent with what have been theoretical considerations on my part. I think that the proarrhythmic effects of sotalol (and presumably with other more or less selective class III agents) manifest as torsades de pointes, rather than the conventional type of proarrhythmic effect (namely, increases in VPCs), which is often difficult to distinguish from the natural variation in the occurrence of the arrhythmia. In the absence of the development of symptoms, it is difficult to call it a proarrhythmic action with complete certainty.

Dr. Deedwania, I have a question about the relationship between lengthening of the action potential duration and the suppression of VPCs. The data available come from several studies that emphasize the importance of β blockers as VPC suppressants. For example, a multicenter study comparing quinidine and acebutolol[1] resulted in no significant difference in efficacy. The data from Dr. Mahmarian's center showed that quinidine and sotalol did not appear to differ very much in terms of suppression of total VPCs[2]; your data show a trend, at least for the total VPC count, but not a big difference between couplets or repetitive forms or VT events, which really is the crucial issue with sotalol. Would you comment on these apparent discrepancies in data relative to the question of whether there is a real difference between the effects of a conventional β blocker and sotalol in suppressing VPCs? In addition, if there is indeed more than a statistical difference, how does one account for it?

Dr. Prakash Deedwania (Fresno, California): First, there is a difference when one compares propranolol with sotalol; overall, sotalol is more effective in suppressing VPCs. As I mentioned, the patients in this study were not selected because of having high-frequency repetitive ventricular ectopy or VT. However, although we cannot prove it, the class III action of sotalol could contribute to

the overall effect in suppressing VPCs and repetitive ectopy. Alternatively, there may be an effect on conduction, which may be more marked in diseased or scarred tissue as might occur in infarction. Dr. Singh, you might have other explanations.

Dr. Bramah Singh: Not at all, although it intrigues me. However, if you postulate the involvement of a class I effect in diseased tissues and at high concentrations, it is a possibility. Why 1 compound (e.g., clofilium) that lengthens repolarization markedly has no VPC suppressant effect and another like sotalol, which appears to be more potent than a conventional β blocker, has a significant effect is still not known. d-Sotalol may give us a real opportunity to define the relative importance of β blockade vs the class III effect of the drug in different subsets of arrhythmia patients, especially those with VPCs.

Dr. Deedwania: I am not sure whether it will be easy to differentiate the relative effects of class III vs β-blocker effects by using d-sotalol. We noted that, in patients with high heart rate, there were no differences between propranolol and sotalol, whereas in those who started with heart rate less than 75 beats/min, the sotalol group did better. This indicates that some unique property of the drug, possibly class III action, explains the greater effect.

Question: Did the doses employed for sotalol and propranolol have equivalent β-blocking effects?

Dr. Deedwania: Yes. I did not show the data for the entire 24-hour period with respect to the mean heart rate; the values were very comparable and there was equivalent β blockade by both drugs.

Dr. Bramah Singh: I must emphasize, however, that to choose precisely the equivalent β-blocking doses of 2 antagonists is notoriously difficult by the use of resting heart rate alone. It would be prudent also to subject a group of patients to exercise to arrive at equivalent doses with a greater measure of certainty. Dr. Antonaccio, as a professional pharmacologist, what are your thoughts?

Dr. Michael Antonaccio (Wallingford, Connecticut): I do not believe that is really important, because when he doubled the dose of propranolol, there was no further increase in efficacy, whereas when he doubled the dose of sotalol, there was a doubling of efficacy. Therefore, I believe that it really is irrelevant in this particular trial.

Dr. Reiffel: I have just 1 caveat. In our d-sotalol experience with supraventricular arrhythmias,[3] we noticed that a substantial minority of patients developed cycle-length-related, left bundle branch block with premature contractions. Therefore, I am a little concerned about Holter judgments of VPC counts without a really precise delineation that these complexes were not supraventricular in origin. In other words, I suggest that we look at both atrial and ventricular extrasystoles to be sure that we are not merely confusing the configuration of atrial beats and miscounting them as ventricular.

Dr. Deedwania: Are you saying that during a 24-hour period, occasionally a left bundle branch block comes and goes intermittently?

Dr. Reiffel: Yes, we had 3 or 4 such patients. Of 10 patients on d-sotalol, atrial ectopy was noted to have a left bundle configuration consistently through the day and that was not present in the control state; I suspect it is because with the action potential duration and refractory period prolongation this might occur.

Dr. Deedwania: At the point when the patients here had Holter evaluations, they also had a 12-lead electrocardiogram with a long rhythm strip. They did not have any obvious left bundle branch block or any other intraventricular conduction defect. If they did, then obviously there would be difficulties.

Dr. Bramah Singh: I have a little problem with the conclusions with respect to the finding that there was no selectivity of suppression of repetitive VPCs by propranolol or sotalol. In our experience with giving sotalol to patients with more malignant arrhythmias, some of whom had VT, sotalol eliminated the runs of nonsustained VT. We have had a similar experience with nadolol.[4] I believe that perhaps the differences noted might reflect differences in patient populations.

Dr. Deedwania: I agree with you.

REFERENCES

1. Chandraratna PAN. Comparison of acebutolol with propranolol, quinidine, and placebo. Results of three multicenter arrhythmia trials. *Am Heart J 1985;109:1198–1204.*

2. Mahmarian JJ, Verani MS, Hohman T, Hill R, Thornton BC, Bolli R, Young JB, Roberts R, Pratt CM. The hemodynamic effects of sotalol and quinidine: analysis of use of rest and exercise gated radionuclide angiography. *Circulation 1987;76:324–331.*

3. Sahar DI, Reiffel J, Bigger TJ, Equatrito A, Kidwell GA. Efficacy, safety and tolerance of d-sotalol in patients with refractory supraventricular tachyarrhythmias. *Am Heart J 1989;117:562–568.*

4. Nademanee K, Schleman MM, Singh BN, Morganroth J, Reid PR, Stritar JA. Beta-adrenergic blockade by nadolol in the control of ventricular tachyarrhythmias. *Am Heart J 1984;108:1109–1115.*

Effects of Sotalol on Ventricular Tachycardia and Fibrillation Produced by Programmed Electrical Stimulation: Comparison with Other Antiarrhythmic Agents

Koonlawee Nademanee, MD, and Bramah N. Singh, MD, DPhil

Sotalol, a β blocker, is now recognized as an important class III agent. The drug lengthens the action potential in most cardiac tissues without affecting conduction. Several studies have shown that sotalol is very effective in treating life-threatening arrhythmias. One hundred thirty-eight patients with inducible and clinically sustained tachycardia were retrospectively analyzed. With the use of the $S_1S_2S_3$ stimulation protocol for ventricular tachycardia (VT) induction, sotalol prevented VT/ventricular fibrillation (VF) induction in 45% of the patients; other class I agents prevented VT/VF induction in only 15 to 22%. Data were also analyzed from a prospective multicenter study comparing sotalol with procainamide in suppressing sustained VT in 153 patients with symptomatic sustained VT/VF. With the use of the $S_1S_2S_3S_4$ stimulation protocol, sotalol prevented VT/VF induction in 35% of the patients, whereas procainamide prevented VT/VF induction in only 22% (difference not significant). When patients whose VT induced by the triple-stimuli protocol were excluded, sotalol prevented VT induction in 53%. These findings indicate that the antiarrhythmic effects of sotalol are comparable to those of class I agents in treating malignant arrhythmias. Although more data are needed on the comparative effects of sotalol, available data establish sotalol as an important addition to available antiarrhythmic agents.

(Am J Cardiol 1990;65:53A–57A)

From the Department of Cardiology, West Los Angeles Veterans Administration Medical Center, and the Department of Medicine, University of California Los Angeles School of Medicine, Los Angeles, California.

Address for reprints: Koonlawee Nademanee, MD, Cardiology Section 691/W111E, West Los Angeles Veterans Administration Medical Center, Wilshire and Sawtelle Boulevards, Los Angeles, California 90073.

Several new antiarrhythmic agents introduced in recent years have significantly advanced the treatment of life-threatening cardiac arrhythmias.[1] Of these, compounds that lengthen repolarization—class III agents—intrigue electrophysiologists and cardiologists alike. The surge of interest in these compounds stems in part from the widespread attention in the early 1980s to a particular class III agent: amiodarone.[2,3] Despite its well-known adverse effects, amiodarone continues to be widely used because it is a remarkably effective antiarrhythmic agent for patients with malignant ventricular arrhythmias. Initially, amiodarone was believed to exert its antiarrhythmic effects primarily by lengthening cardiac repolarization.[4] However, recent data indicate that amiodarone has, in fact, a more complex array of electrophysiologic (EP) effects: weak sodium-channel blocking, calcium antagonistic, and nonspecific sympathetic blocking effects.[5] Thus, one cannot attribute amiodarone's antiarrhythmic effects to its action on repolarization alone.

Nevertheless, it appears that the lengthening of cardiac repolarization as a discrete antiarrhythmic effect is an idea whose time has come.[4–6] In the search for new compounds with class III antiarrhythmic effects, sotalol has emerged as a promising agent.[7] Sotalol, which is also a β-blocking agent, is actually a purer class III agent than amiodarone.[8] Therefore, if the lengthening of cardiac repolarization is an important antiarrhythmic effect, sotalol should be more effective in treating various cardiac arrhythmias. In this report, we compare the effects of sotalol with those of other antiarrhythmic agents and critically evaluate the compound's effectiveness as an antiarrhythmic for treating malignant ventricular arrhythmias. We focus on published reports,[9,10] our data, and data from a multicenter study comparing the effects of sotalol with those of procainamide.

COMPARISON OF ELECTROPHYSIOLOGIC EFFECTS OF SOTALOL WITH OTHER ANTIARRHYTHMIC AGENTS

Although sotalol was introduced as a β-adrenergic blocking agent, its EP effects differ markedly from those of other β blockers[8]; the details are provided elsewhere in this symposium.[11] Administered acutely, sotalol lengthens the action potential duration with concomitant lengthening of the effective and absolute refractory periods of ventricular muscle in a dose-dependent manner[12] (Table I); in contrast, other β blockers have no acute

TABLE I Electrophysiologic Characteristics of Sotalol Versus Other Antiarrhythmic Agents

Parameters	Sotalol	Propranolol	Amiodarone	Type 1A	Type 1B	Type 1C
Action potential duration	Marked increase	No change	Marked increase	Increase	No change	Variable
Ventricular ERP	Increase	No change	Increase	Increase	Decrease	Increase
V_{max}	No change	No change	Decrease during fast rate	Decrease	No change	Marked decrease
Autonomic effects	β blockade	β blockade	Antisympathetic	Antivagal	None	None
Local anesthetic	No	Yes	Yes	Yes	Yes	Yes

ERP = effective refractory period.

effects on repolarization.[13] Therefore, the effects of sotalol on repolarization are unlikely to be mediated by the compound's antiadrenergic effects.[14]

Sotalol and amiodarone have similar effects on repolarization during chronic drug administration. Sotalol differs from amiodarone in not affecting the upstroke velocity of phase 0 (V_{max}) of the action potential—the local anesthetic effect. Amiodarone suppresses the V_{max} rapidly—the use-dependent block. Sotalol differs from all class I antiarrhythmic agents in this regard (Table I). Sotalol increases the effective refractory period, sinus cycle length, atrioventricular nodal conduction and the His-Purkinje conduction of atrial and ventricular muscle,[10] but does not affect QRS and HV intervals.

EFFECTS OF SOTALOL IN LIFE-THREATENING VENTRICULAR ARRHYTHMIAS

The role of sotalol in treating patients with recurrent ventricular tachycardia/ventricular fibrillation (VT/VF) has been evaluated recently.[9,10] Two systematic unblinded studies[9,10] have provided data on the efficacy of sotalol in controlling refractory VT/VF.

SOTALOL AND INDUCIBILITY OF VENTRICULAR TACHYCARDIA

Senges et al[9] performed EP testing in 18 patients before and after administration of an intravenous 1.5–mg/kg dose of sotalol with double stimuli for VT/VF induction. In this study, sotalol prevented reinduction of the tachycardia in 12 of 18 patients (67%). The effect on inducibility was not systematically related to the lengthening of the QTc interval. Nine of these 12 patients were given oral sotalol, and 4 other patients were given another regimen. Of these 13 patients, 12 had successful long-term effects and 1 had partial response over a mean follow-up period of 16 months (range 8 to 24). Heart failure or sinus node dysfunction developed in 3 patients during the early months of treatment. The investigators concluded that sotalol's overall antiarrhythmic response was not typical of β blockers; they related sotalol's observed effects to its property of prolonging the cardiac action potential duration. Our experience supports these data.[8]

We investigated the effects of sotalol in preventing inducible VT and the long-term effects of chronic, oral sotalol therapy in controlling recurrent arrhythmias. We studied 37 patients (36 men, 1 woman; mean age 58 years, range 25 to 72) with clinically sustained recurrent VT/VF. None had a reversible cause of ventricular arrhythmias or recent (in the 4 weeks immediately preceding the study) myocardial infarction. Except for 1 patient with sarcoidosis, all patients had coronary artery disease. The mean left ventricular ejection fraction in 23 patients, measured with either contrast or radionuclide ventriculography, was 33.0 ± 14.0%. Patients were excluded who exhibited contraindication to β blockade or evidence of decompensated cardiac failure. Two patients whose VT could not be induced at baseline (see later) were also excluded. Treatment in all patients except 1 was unsuccessful or ≥1 (mean 2.76 ± 1.3) conventional antiarrhythmic drugs could not be tolerated. Intravenous sotalol was given to 2 patients with frequent and recurrent VT/VF who had not responded to intravenous lidocaine, procainamide and bretylium tosylate. However, these patients did not undergo EP studies either before or after drug administration because of clinical exigencies. Sotalol controlled these patients' incessant VT/VF.

Of the 35 patients who had undergone EP testing, 33 had inducible VT/VF. A 1.5–mg/kg intravenous dose of sotalol prevented VT/VF reinduction in 15 patients (45.5%). Twenty-five of the 33 patients (15 had positive and 10 had negative results on EP testing) were given oral sotalol (dose range of 160 to 460 mg twice a day).

The clinical outcome of patients with inducible vs noninducible VT/VF were evaluated after intravenous and subsequent oral sotalol therapy. Intravenous sotalol prevented inducible VT/VF in 15 patients. Oral sotalol controlled the arrhythmias in 13 of these patients (86.7%). Sotalol had no effect early (within the first month) in 1 patient and appeared to aggravate the condition in another. During chronic therapy (longer than 1 month), the arrhythmia recurred in 2 patients (at 8 and 8.4 months); adverse effects precluded continued use of the drug in another 2 patients. Eight patients remained arrhythmia-free and had no adverse effects during a mean follow-up period of 14.5 ± 7.5 months (range 2 to 23). Sotalol was unable to suppress VT/VF in 18 patients. Of these, 10 were given oral sotalol; the other 8 were not treated with sotalol because they did not have significant ventricular premature complexes (VPCs) on baseline ambulatory electrocardiographic recordings. Six of the 10 who were given oral sotalol had recurrent VT/VF and 1 had a limiting adverse effect, despite the inducible VT after intravenous sotalol. The remaining 3 patients have been free of arrhythmias (mean follow-up

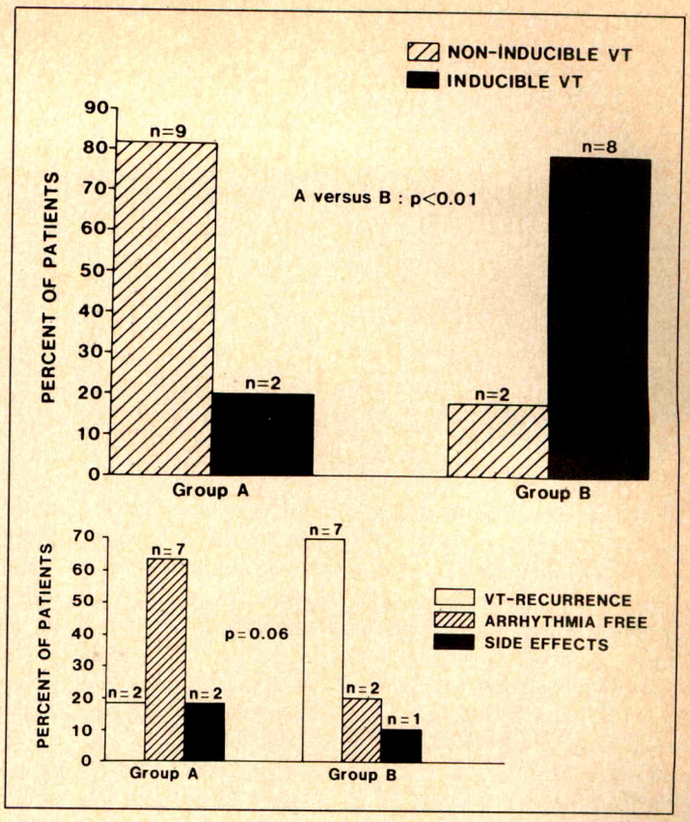


FIGURE 1. ***Top,*** **relation between the effects of intravenous sotalol on the inducibility of ventricular tachycardia/ventricular fibrillation (VT/VF) and the degree of suppression by the oral drug of the spontaneously occurring ventricular arrhythmias in the same patients. Group A patients: Administration of sotalol resulted in 85% suppression of total ventricular premature complexes (VPCs) and 90% suppression of paired VPCs and beats of VT. Group B: Sotalol did not have these effects. Note that the number of patients in whom sotalol prevented reinduction of VT/VF was significantly higher in group A than in group B.** ***Bottom,*** **differences in the clinical outcome in patients relative to the degree of suppression of spontaneously occurring arrhythmias during Holter monitoring. The separation of patients into groups A and B follows the same criteria as in (*top*). The difference between the 2 groups is of borderline significance. The data presented suggest that the prevention of inducible VT/VF by intravenous sotalol and the suppression of spontaneously occurring arrhythmias by oral sotalol are both predictive of long-term clinical outcome of prophylactic sotalol therapy in patients with ventricular tachyarrhythmias. (Reproduced with permission of the *American Heart Association.*)**

period 8.6 months, range 8 to 9). The 6 patients treated with 160 mg of oral sotalol twice a day had mean plasma levels of 2.3 ± 0.8 μg/ml. The 3 patients treated with 320 mg of oral sotalol twice a day had mean plasma levels of 3.1 ± 0.4 μg/ml.

HOLTER VERSUS ELECTROPHYSIOLOGIC TESTING TO PREDICT LONG-TERM OUTCOME OF SOTALOL THERAPY

Our data from 21 patients who underwent 24-hour Holter recordings before and during steady-state oral sotalol therapy showed that sotalol reduced the total VPC count by 73% ($p < 0.01$), paired VPCs by 89% ($p < 0.01$), and VT beats by 95% ($p < 0.01$).[10] In 11 patients, sotalol reduced total VPCs by at least 85%, and paired VPCs and VT beats by at least 90% (group A). In the remaining 10 patients, sotalol did not significantly suppress spontaneously occurring arrhythmias (group B). Sotalol prevented reinduction of VT in 9 patients in group A but not in the other 2 patients. In contrast, VT remained inducible in 8 patients in group B. The Fisher exact test showed significantly more patients with noninducible VT in group A than in group B ($p < 0.01$). Moreover, only 2 patients in group A (18%) had recurrent VT/VF compared with 7 patients in group B (70%). Two patients in group A and 1 patient in group B had significant adverse effects, necessitating discontinuation of the drug.

In our study,[10] intravenous sotalol prevented the reinduction of VT/VF in 45.5% of patients. This figure is generally higher than that reported for class I compounds.[15] Data are scant on this effect for other class III agents; however, data show that amiodarone prevents reinduction of VT/VF after chronic therapy in 8 to 50% of cases.[16] Senges et al[9] recently demonstrated that intravenous sotalol prevented VT/VF reinduction in 12 of 18 patients (67%). This is a higher success rate than in our own series, in which 15 of 33 patients became noninducible after receiving sotalol intravenously. In Senges' study, 9 of 12 patients subsequently treated with oral sotalol remained in complete or partial control over a mean follow-up period of 16 months. This is in accord with our data on chronic oral therapy, which indicated the clinical usefulness of EP testing in predicting the long-term effectiveness of oral sotalol in controlling VT/VF.

Our data also demonstrate that orally administered sotalol is moderately effective in suppressing VPCs, particularly the complex and repetitive forms. In over 50% of the study patients, sotalol suppressed at least 85% of total VPC counts and abolished almost all complex beats, i.e., paired VPCs and VT beats (Fig. 1).

SOTALOL VERSUS OTHER ANTIARRHYTHMIC AGENTS IN VENTRICULAR TACHYCARDIA INDUCTION USING DOUBLE STIMULI: A RETROSPECTIVE ANALYSIS

Patient population: The study examined 138 patients with clinically sustained VT or VF, or both. Most (117) had coronary artery disease. VT was inducible in all patients (102, sustained VT; 36, nonsustained VT). Patients whose VT could be induced only by triple stimuli ($S_1S_2S_3S_4$) were excluded.

TABLE II Comparison of Sotalol with Other Antiarrhythmic Agents on the Suppression of Ventricular Tachycardia

Test Drug By Class	No. of Patients (Not Inducible)	% Effective Test
Class IA		
Quinidine	16 (1)	6
Procainamide	31 (6)	19
Class IB		
Lidocaine	17 (4)	23
Mexilitene	11 (2)	18
Class IC		
Flecainide	8 (1)	12
Encainide	7 (1)	14
Recainam	6 (1)	17
Propafenone	6 (0)	0
Class III		
Sotalol	33 (15)	45
Amiodarone	54 (21)	39

Electrophysiologic study: The stimulation protocol was described previously.[10] EP studies were performed after the patients had discontinued taking antiarrhythmic agents for 5 half-lives in the control group, and during the steady-state drug concentration of antiarrhythmic treatment.

Antiarrhythmic agents: Table II lists drug tests for the 138 patients and the number of patient testings for each drug. The number of patient testings is larger than 138 because some patients had undergone more than 1 drug test. For quinidine, all 16 patients were given 10 mg/kg intravenously. For procainamide, 31 patients were tested with intravenous administration at a loading dose of 15 mg/kg followed by a 3–mg/min maintenance infusion.

Results: Table II summarizes the results of drug testing for the suppression of inducible VT by programmed electrical stimulation. Sotalol prevented VT induction in 45% of patients. This was the highest success rate of all of the antiarrhythmic agents. The second most effective agent, amiodarone, prevented VT induction in 39% of patients, but this was not significantly different from that produced by sotalol. Class IC agents had the lowest efficacy.

SOTALOL VERSUS PROCAINAMIDE: A PROSPECTIVE MULTICENTER STUDY

A double-blind, randomized, multicenter study comparing the effects of sotalol and procainamide in both intravenous and oral forms was recently completed. Preliminary data, previously presented in abstract form,[17] are briefly discussed here; the definitive report will be published elsewhere by the Multi-Center Sotalol Research Group. Patients with recurrent VT/VF underwent EP studies with programmed electrical stimulation. Patients with inducible VT/VF were randomized to receive either procainamide (n = 49) or sotalol (n = 54) in a blinded fashion using a third-party blinder.

The EP protocol required using at most triple stimuli, 1 site, and at least 3 cycle-length ventricular pacing rates to determine VT inducibility. Intravenously administered procainamide (plasma level 7.8 ± 2.3 μg/ml) prevented reinduction of VT/VF in 11 patients (22%), as did sotalol (plasma level of 2.14 ± 0.40 μg/ml) in 18 patients (33%); the difference was not statistically significant. If data analysis was based strictly on the criteria of inducible VT only by double stimuli ($S_1S_2S_3$) and excluding all patients whose VT was induced only by triple stimuli, intravenous

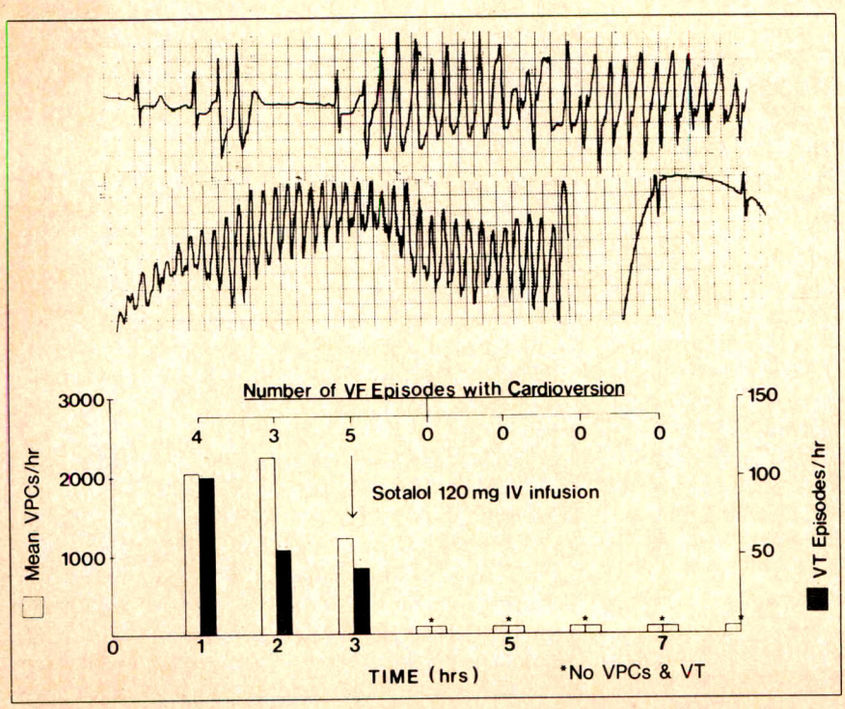


FIGURE 2. Effects of intravenous sotalol in a patient with recurrent ventricular tachycardia/ventricular fibrillation (VT/VF) resistant to lidocaine, procainamide and bretylium. *Top*, characteristic patterns of incessant VT uncontrolled by conventional therapy. *Bottom*, changes in the total ventricular premature complex (VPC) count and number of VT episodes before and after the intravenous injection of sotalol. Note that after sotalol was given, there were no further recurrences of VT/VF. (Adapted with permission from the *American Heart Association*.)

procainamide prevented VT induction in 34% and sotalol in 53% ($p = 0.21$). These data are similar to those in our series subjected to retrospective analysis. In fact, sotalol had a higher percentage of success by double-stimuli criteria.

DISCUSSION

Further evaluation of sotalol is needed to obtain a better understanding of its role in the treatment of malignant ventricular arrhythmias. Clearly, the EP effects of intravenous sotalol differ significantly from those of conventional β blockers. Sotalol markedly increases the effective refractory period in the atria, ventricles and His-Purkinje system. Unlike conventional β blockers, sotalol can prevent inducibility of VT/VF produced by programmed electrical stimulation. In fact, when double extrastimuli were used to gauge effect, sotalol was comparable to other antiarrhythmic agents (range 45 to 67%) (Table I). Our data also show that programmed electrical stimulation had high predictive accuracy for favorable clinical outcome during long-term oral sotalol therapy.

The data also suggest that class III agents, i.e., sotalol and amiodarone, may be more effective than other classes of antiarrhythmic agents in preventing VT/VF induction. However, amiodarone's effect on the inducibility of VT/VF and the subsequent clinical outcome remains controversial. The data on sotalol—although more limited—are more consistent; sotalol provides a greater degree of protection than class I antiarrhythmic compounds. Nevertheless, we suggest caution in interpreting these data in the absence of large prospective, controlled clinical trials.

Although these data did not show statistically that sotalol is better than procainamide, there is a trend suggesting that if the patient sample size were larger, the difference could be statistically significant. However, the data do confirm previous clinical observations and animal studies that the class III effects of sotalol are beneficial for treating life-threatening ventricular tachyarrhythmias.

The associated antisympathetic and antifibrillatory properties of sotalol should be emphasized. Because of its inherent β-blocking effects, sotalol is probably a more useful agent than class I antiarrhythmic drugs for any ischemia-related arrhythmia. In addition, because it is known that increased sympathetic activity during myocardial ischemia enhances VT/VF,[18] sotalol, because of its β-blocking properties, should be an excellent choice for treating both catecholamine-induced and ischemia-associated arrhythmias. The drug is particularly effective in controlling persistent VF. Figure 2 illustrates the effects of intravenous sotalol in a patient with incessant ventricular flutter and fibrillation that had proved to be resistant to lidocaine, procainamide and bretylium. This patient had several episodes of VF, necessitating multiple cardioversions. Sotalol infusion abolished all VT/VF episodes. This suggests that the drug not only suppressed spontaneously occurring malignant ventricular arrhythmias, but also increased the VF threshold in this patient. The same results were found in 2 other patients with incessant VT/VF.

This observation is supported by other findings. Lynch et al[19] observed that sotalol significantly reduced the incidence of VF in their conscious-dog ischemic model of sudden coronary death. Marshall et al[20] found that sotalol, when given intravenously, significantly increased the VF threshold in both normal and ischemic myocardium in the anesthetized rat. Metoprolol, a cardioselective β blocker that does not lengthen cardiac repolarization, had no effect on VF threshold in the normal myocardium and prevented a decrease in VF threshold only after coronary occlusion.[20] These findings, along with those of Patterson and Lucchesi,[21] underscore the overall antifibrillatory and antiarrhythmic actions of sotalol.

REFERENCES

1. Nademanee K, Singh BN. Advances in antiarrhythmic therapy: the role of newer antiarrhythmic agents. *JAMA 1981;247:2:217–222.*

2. Nademanee K, Singh BN, Hendrickson JA, Intarrachot V, Lopez B, Feld G, Cannom D, Weiss J. Amiodarone in refractory life-threatening ventricular arrhythmias. *Ann Intern Med 1983;98:577–584.*

3. Heger JJ, Prystowsky EN, Jackman WM, Naccarelli G, Warfel K, Rinkenberger R, Zipes D. Amiodarone: clinical efficacy and electrophysiology during long-term therapy for recurrent ventricular tachycardia or ventricular fibrillation. *N Engl J Med 1981;305:539–545.*

4. Singh BN, Nademanee K. Control of cardiac arrhythmias by selective lengthening of repolarization: theoretic considerations and clinical observations. *Am Heart J 1985;109(2):421–430.*

5. Mason J. Amiodarone. *N Engl J Med 1987;316:455–464.*

6. Singh BN, ed. Control of Cardiac Arrhythmias by Lengthening Repolarization. *Mt Kisco, New York: Futura Publishing, 1988.*

7. Singh BN. Control of cardiac arrhythmias by lengthening repolarization: unique role of sotalol. In: Sami M, ed. Advances in Cardiology: The Unique Role of Sotalol. *Oxford: The Medicine Publishing Foundation, 1985:15–30.*

8. Singh BN, Nademanee K. Sotalol: a beta-blocker with unique antiarrhythmic properties. *Am Heart J 1987;114:121–139.*

9. Senges J, Lengfelder W, Jauernig R, Czyfan E, Brachmann J, Rizos I, Cobbe S, Kubler W. Electrophysiologic testing of therapy with sotalol for sustained ventricular tachycardia. *Circulation 1984;69:577–583.*

10. Nademanee K, Feld G, Hendrickson JA, Singh PN, Singh BN. Electrophysiologic and antiarrhythmic effects of sotalol in patients with life-threatening ventricular tachyarrhythmias. *Circulation 1985;72:555–564.*

11. Singh BN. Historical development of the concept of controlling arrhythmias by lengthening repolarization: particular reference to sotalol. *Am J Cardiol 1990;65:3A–11A.*

12. Echt DS, Berte LE, Clusin WT, Samuelsson RG, Harrison DC, Mason JW. Prolongation of the human cardiac monophasic action potential by sotalol. *Am J Cardiol 1982;50:1082–1086.*

13. Edvardsson N, Hirsch L, Emmanuelsson H, Ponten J, Olsson SB. Sotalol induced delayed ventricular repolarization in man. *Eur Heart J 1980;1:335–340.*

14. Kato R, Yabek S, Ikeda N, Kannan R, Singh BN. Electrophysiologic effects of dextro- and levo-isomers of sotalol in isolated cardiac muscle and their in vivo pharmacokinetics. *JACC 1986;7:116–125.*

15. Horowitz LN, Josephson ME, Kastov JA. Intracardiac electrophysiologic studies as a method for the optimization of drug therapy in chronic ventricular arrhythmias. *Prog Cardiovasc Dis 1980;23:81–98.*

16. Horowitz LN, Spielman SR, Greenspan AM, Webb CR, Kay HR. Ventricular arrhythmias: use of electrophysiologic studies. *Am Heart J 1983;106:881–890.*

17. Nademanee K, Lee IK, Singh BN. Sotalol versus procainamide in the prevention of ventricular tachycardia induction: a double-blind parallel multicenter study. *Presented at the American Heart Association 59th Scientific Sessions in Dallas, Texas, November 1986.*

18. Zipes DP, Levy MN, Cobb LA, Julius S, Kaufman PG, Miller N, Verrier R. Task Force 2: Sudden cardiac death. Neural-cardiac interactions. *Circulation 1987;76:1:202–207.*

19. Lynch JJ, Coskey LA, Montgomery DG, Benedict BR. Prevention of ventricular fibrillation by dextrorotatory sotalol in a conscious canine model of sudden coronary death. *Am Heart J 1985;109:949–958.*

20. Marshall RJ, Muir AW, Winslow E. Effects of antiarrhythmic drugs on ventricular fibrillation thresholds of normal and ischemic myocardium in the anesthetized rat. *Br J Pharmacol 1983;78:165–171.*

21. Patterson E, Lucchesi BR. Antifibrillatory properties of the beta adrenergic receptor antagonists, nadolol, sotalol, atenolol and propranolol in the anesthetized dog and rabbit cardiac tissue. *Pharmacology 1984;28:121–129.*

Safety and Efficacy of Sotalol in Patients with Drug-Refractory Sustained Ventricular Tachyarrhythmias

Richard F. Kehoe, MD, Terry A. Zheutlin, MD, Cathy S. Dunnington, RN, MS, Thomas A. Mattioni, MD, George Yu, PhD, and Robert B. Spangenberg, MD, PhD

The safety and efficacy of oral sotalol, an investigational β-adrenergic blocker with class III antiarrhythmic drug properties, were examined in a multicenter study in 236 patients with sustained ventricular tachyarrhythmias. In 104 patients, the index arrhythmia was a cardiac arrest, and all patients had undergone at least 3 previous unsuccessful antiarrhythmic trials (mean = 5 per patient). In the 106 patients assessed by programmed electrical stimulation, sotalol completely suppressed induction of ventricular tachycardia (VT) in 33 (31%) and rendered VT slower (>100 ms prolongation of cycle length) or more difficult to induce in 29 (27%). Using continuous 24-hour ambulatory monitoring methods, sotalol complete- and partial-response rates were 51 and 12%, respectively.

Of the 236 acute-phase patients, 151 were discharged receiving long-term sotalol therapy. The median sotalol dose was 480 mg/day. At a mean follow-up of 346 ± 92 days, 27 patients (18%) had recurrence of sustained arrhythmia; 9, sudden death; 11, sustained VT; 5, automatic defibrillator discharge; and 2, syncope. Adverse effects forced discontinuation of therapy in 10 patients (7%): 6 secondary to symptomatic bradyarrhythmia, 2 due to refractory heart failure, 1 due to torsades de pointes, and 1 from bronchospasm. Life-table analysis of sotalol's overall long-term efficacy at 6, 12 and 18 months were 80, 76 and 72%, respectively. Although mean follow-up was short (<1 year), neither acute-phase programmed stimulation nor 24-hour ambulatory monitoring responses were significantly predictive of subsequent arrhythmic outcome.

Proarrhythmia was documented in 18 patients (7%), 17 during the acute phase and 1 during long-term follow-up. Proarrhythmia was manifested as torsades de pointes in 11 patients and as an increase in sustained VT episodes in 7. Of the 18 proarrhythmic complications, 14 (78%) occurred within 7 days of therapy. Symptomatic bradycardia occurred in 8 patients (3%) (7 during the acute phase, 1 long-term) and aggravation of heart failure in 7 (3%) (6 acute phase, 1 long-term).

Thus, sotalol appears to be an effective agent for suppressing refractory, sustained ventricular tachyarrhythmias and is well tolerated during long-term therapy. Proarrhythmia was observed in 7% of patients and tended to occur during the acute titration phase. Accordingly, it is recommended that patients with sustained ventricular tachyarrhythmias treated with sotalol be observed under continuous electrocardiographic monitoring until acute-phase dose titration has been completed.

(Am J Cardiol 1990;65:58A–64A)

Sotalol is a noncardioselective β-adrenergic blocking agent that also exerts potent class III antiarrhythmic effects.[1,2] These properties suggest that it would be useful for managing patients with life-threatening ventricular tachyarrhythmias. Previous clinical studies, which have been generally limited to relatively small numbers of patients, have shown that sotalol administration produces a reduction in the frequency of ventricular premature beats,[3–6] suppresses ventricular tachycardia (VT) induction in response to programmed electrical stimulation (PES),[7–9] and prevents arrhythmic recurrence in patients presenting with sustained VT or ventricular fibrillation (VF).[8–12] Because of these promising preliminary findings, a multicenter open-label trial was undertaken to determine the safety and efficacy of oral sotalol in patients with drug-refractory sustained ventricular tachyarrhythmias. The results of this study are reported here.

In addition to the safety and efficacy considerations just mentioned, a secondary purpose of this study was to determine which arrhythmia assessment technique, PES or ambulatory monitoring, provided the more accurate prognostic information concerning arrhythmia recurrence.

From the Clinical Cardiac Electrophysiologic Laboratory, Section of Cardiology, Department of Medicine, Northwestern University School of Medicine and the Sotalol Ventricular Tachycardia Study Investigators (see Appendix); and the Departments of Biostatistics/Data Management and Cardiovascular Clinical Research, Bristol-Myers Company, Pharmaceutical Research and Development Division, Wallingford, Connecticut. This study was supported in part by a grant from Bristol-Myers Company, Pharmaceutical Research and Development Division, Wallingford, Connecticut.

Address for reprints: Richard F. Kehoe, MD, Illinois Masonic Medical Center, 836 Wellington Avenue, Chicago, Illinois 60657.

METHODS

Between January 1984 and September 1987, 236 patients at 28 centers throughout the United States and Canada (see Appendix) received oral sotalol for ventricular tachyarrhythmias. All fulfilled the following inclusion criteria: (1) documented, symptomatic, sustained VT or VF; (2) inefficacy or intolerance or both, to at least 3 previously administered antiarrhythmic drugs; and (3) the index arrhythmia unrelated to acute infarction, electrolyte disturbances, apparent drug-mediated proarrhythmia or other reversible factors. Exclusion criteria included the following: (1) left ventricular ejection fraction <25%; (2) congestive heart failure unresponsive to conventional therapy; (3) asthma or chronic obstructive lung disease requiring a bronchodilator; (4) a prior adverse reaction to β-adrenergic blockers; (5) a resting bradycardia of <50 beats/min; (6) a resting QTc interval >450 ms; and (7) need for concomitant therapy with agents that lengthen the QT interval (e.g., tricyclic antidepressants or amiodarone). The clinical characteristics of the study population and the prior antiarrhythmic therapy used are summarized in Tables I and II, respectively.

Study design: All antiarrhythmic drugs, with the exception of amiodarone, were discontinued for a minimum of 5 elimination half-lives before instituting sotalol therapy. Amiodarone had to be discontinued for 30 days or until the serum concentration was less than 0.3 μg/ml before initiating sotalol therapy. Therapy with digoxin was continued when used for the treatment of congestive heart failure. After qualifying for enrollment in this study, all patients underwent continuous 24-hour ambulatory monitoring and, at the discretion of the investigator, a PES (106 patients) in the drug-free baseline state. Thereafter, the investigator was required to select the arrhythmia assessment that would be used to make a determination of acute-phase efficacy. The methods available included PES, 24-hour ambulatory monitoring and the suppression of arrhythmic symptoms. For PES to qualify as an acceptable technique, it was required that the patient exhibit the reproducible (× 2) induction of sustained VT during drug-free PES. To qualify for assessment by 24-hour ambulatory monitoring, the patient was required to have an average of 720 isolated ventricular premature complexes per 24 hours and at least 1 spontaneous VT run with a rate of at least 120 beats/min. In patients who fulfilled neither the PES nor the 24-hour ambulatory monitoring criteria, the suppression of arrhythmic symptoms could be used to determine efficacy when VT episodes caused syncope or near-syncope at a frequency of at least 1 episode per week during the month before the initiation of therapy. Patients who could not be assessed by any of the 3 methods described were designated as nonassessable and were referred for empiric therapy.

Sotalol was administered orally, initially at a dose of 80 to 160 mg every 12 hours. Thereafter, upward dose adjustments at intervals of 72 hours could be undertaken in a stepwise fashion to levels of 240 mg every 12 hours, 320 mg every 12 hours, and finally 480 mg every 12 hours, based on therapeutic response and the emergence of adverse effects. On completion of dose titration, an efficacy was determined and sotalol was either discontinued or the patient was discharged receiving chronic therapy and enrolled in the long-term outpatient phase. Patients could be discharged with chronic sotalol therapy in the absence of a partial or a complete response if the investigator had determined that no other therapeutic options were feasible. Conversely, in selected patients who exhibited a complete or partial response during the acute phase of therapy, sotalol could be discontinued in favor of other therapeutic alternatives if they appeared to be more suitable for long-term management. After hospital discharge, patients were followed at bimonthly intervals.

Sotalol therapy was deemed ineffective in the long-term outpatient phase and patients were withdrawn from the study if they had symptomatic sustained VT, unexplained syncope, died suddenly (death within 1 hour of the onset of symptoms), experienced discharge of an automatic cardioverter/defibrillator, or had adverse effects serious enough to preclude continuation of sotalol therapy.

TABLE I Characteristics of the Study Population

Clinical Features	
No. of patients	236
Male/female	194/42
Age (years)	59 ± 12
Heart disease type (%)	
ASHD	184 (77)
Prior infarct	168 (71)
Cardiomyopathy	40 (18)
Congenital	12 (5)
Prior CHF	89 (38)
LVEF* (%)	
≥40%	82 (43)
30–40%	62 (30)
20–30%	46 (27)
Arrhythmic features (%)	
Emergency DC cardioversion	186 (79)
Cardiac arrest	104 (44)
Syncope	128 (54)

* Based on 190 patients.
ASHD = atherosclerotic heart disease; CHF = congestive heart failure; DC = direct-current; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

TABLE II Summary of Previous Antiarrhythmic Drug Therapy

No. of patients	236 (%)
Previous drugs	
Procainamide	211 (89)
Quinidine	174 (74)
Disopyramide	68 (29)
Mexiletine	87 (37)
Flecainide	70 (30)
Encainide	9 (4)
Propafenone	51 (22)
Amiodarone	70 (30)
β blockers	97 (41)
Median AA drug failures = 5 ± 1.2 per patient	

AA = antiarrhythmic.

TABLE III Acute-Phase Response to Sotalol as a Function of Arrhythmic Assessment Method

	No. of Pts.	Complete (%)	Partial (%)	None (%)
PES	106	33 (31)	29 (27)	44 (42)
24-hour AM	43	22 (51)	5 (12)	16 (37)
Symptoms	45	19 (42)	6 (13)	20 (45)
Total*	194	74 (38)	40 (21)	80 (41)

* 42 patients were not assessable by any method.
AM = ambulatory monitoring; PES = programmed electrical stimulation.

TABLE IV Long-Term Efficacy, Arrhythmia Recurrence and Adverse Effects in Patients Discharged on Sotalol

No. of patients		151
Mean follow-up (days)		346 ± 92
Median dose (mg/day)		480
Discontinued from study		37 (25%)
Arrhythmic recurrence		27 (18%)
SCD	9	
Sustained VT	11	
AICD discharge	5	
Syncope	2	
Adverse effects		10 (7%)

AICD = automatic implantable cardioverter/defibrillator; SCD = sudden cardiac death; VT = ventricular tachycardia.

Programmed electrical stimulation techniques: PES was undertaken in the drug-free baseline state. The standard stimulation protocol consisted of single, double and triple ventricular extrastimuli delivered to the limits of ventricular refractoriness coupled to driven ventricular cycle lengths of 600, 500 and 400 ms. Stimulation was performed at a current twice the diastolic threshold for capture at a pulse width of 2 ms. All stimulation was initially performed at the right ventricular apex. A second right ventricular stimulation site and burst pacing could be used at the discretion of the investigator if the standard stimulation protocol failed to initiate sustained VT.

Sustained VT was defined as an induced VT with a rate >120 beats/min that lasted for a minimum of 30 seconds or one that required urgent termination in less than 30 seconds because of hemodynamic compromise. The induction of polymorphic VT was accepted as qualifying for inducible VT only in patients whose index arrhythmia was VF.

Criteria for acute-phase efficacy: For patients undergoing PES-directed therapy, the following criteria were used to classify the sotalol response: complete response = suppression of all inducible VT (<10 repetitive ventricular responses); partial response = rendering induced VT nonsustained, more difficult to induce (faster drive-cycle length or more extrastimuli) or if VT cycle length was prolonged by >100 ms; and no response = no change in the pacing stress required to initiate VT or <100 ms prolongation of VT cycle length.

The efficacy criteria used for patients undergoing 24-hour ambulatory monitoring–directed therapy included the following: complete response = ≥75% reduction in isolated ventricular premature beat frequency and ≥60% reduction of total VT beats; and partial response = 50 to 75% reduction in isolated ventricular premature beat frequency and a 40 to 60% reduction of total VT beats.

The efficacy criteria for patients assessed by symptoms included the following: complete response = total suppression of arrhythmic symptoms during a 1-week acute-phase assessment; and partial response = >50% reduction in arrhythmic symptom frequency during the 1-week acute-phase assessment.

Statistical methods: All group data are presented as mean ± standard deviation. Outcome analysis was performed using the nonparametric life-table method and outcomes were compared using the log-rank test. A p value ≤0.05 was considered statistically significant. Sota-

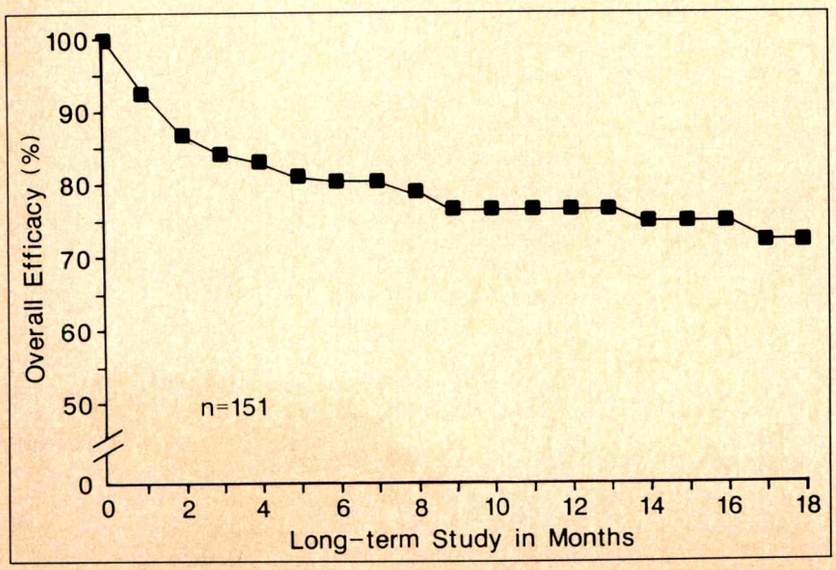


FIGURE 1. Overall long-term phase efficacy of oral sotalol in 151 patients with sustained ventricular tachycardia or ventricular fibrillation. Efficacy was defined as suppression of arrhythmic recurrence and absence of serious adverse effects.

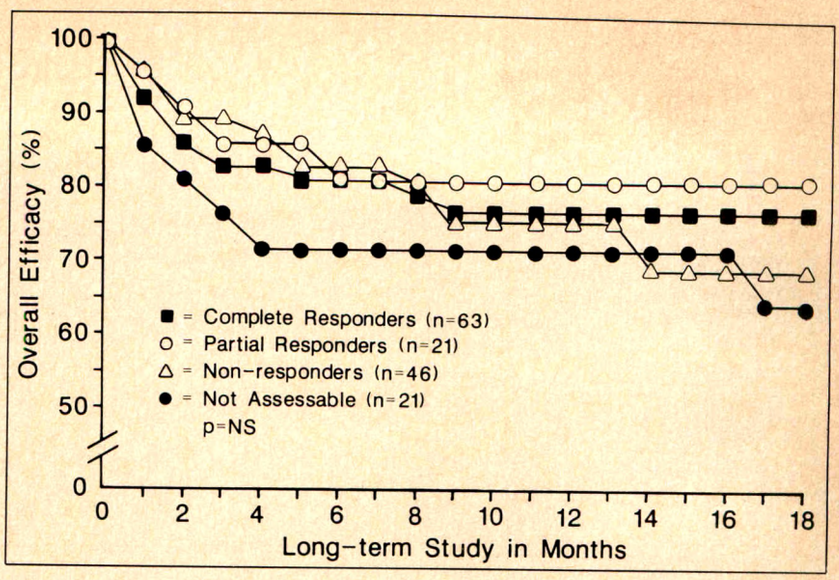


FIGURE 2. Overall long-term phase efficacy of sotalol as a function of acute-phase responses in 151 patients with ventricular tachycardia/ventricular fibrillation. There were no significant differences (NS) in efficacy rates for the 4 groups depicted, although efficacy rates tended to be lower in the nonresponders and nonassessable subgroups.

lol was considered effective during the long-term phase if therapy prevented arrhythmic recurrence and was well tolerated.

RESULTS

Acute-phase responses: Of the 236 patients entering the acute phase, 106 were evaluated by PES, 43 by 24-hour ambulatory monitoring, 45 by symptoms and 42 failed to qualify for assessment by either of these methods. The efficacy of acute-phase sotalol administration is summarized as a function of method of assessment in Table III. Of the 106 patients assessed by PES, 33 (31%) had complete suppression of inducible VT after sotalol administration and 29 (27%) exhibited a partial response. In 44 patients (42%), sotalol did not significantly alter PES responses. Of the 43 patients assessed by 24-hour ambulatory monitoring, 22 (52%) had a complete response, 5 (12%) a partial response and 16 (37%) no response to sotalol administration. In the 45 patients for whom symptoms were used to assess sotalol response, 19 (42%) were classified as complete responders, 6 (13%) as partial responders and 20 (45%) as nonresponders. Overall, 74 patients (38%) were classified as complete and 40 (21%) as partial responders to acute-phase sotalol therapy, whereas 80 patients (41%) were classified as total nonresponders.

Acute-phase adverse effects: Thirty of the 236 acute-phase patients (13%) experienced adverse cardiac effects. Seventeen patients (7%) experienced proarrhythmia that was manifested as torsades de pointes in 10 patients and 7 other events such as presyncope and longer, more frequent runs, etc. Symptomatic bradycardia occurred in 7 patients (3%), whereas 6 patients (3%) had an exacerbation of congestive failure. Proarrhythmia typically occurred early after the initiation of sotalol therapy, 14 of the 17 patients exhibiting this adverse effect on or before day 7 of treatment. Noncardiac adverse effects were not encountered during the acute phase, and none of the adverse effects was fatal.

Long-term phase responses: One hundred fifty-one of the 236 acute-phase patients (64%) were ultimately discharged receiving long-term sotalol therapy at a median dose of 480 mg/day. Of the 151 long-term patients, 63 were classified as acute-phase complete responders, 21 as partial responders and 46 as nonresponders; the remaining 21 patients were nonassessable. At a mean follow-up of 346 ± 92 days, 37 patients (25%) were withdrawn from the study: 27 (18%) because of arrhythmia recurrence and 10 (7%) because of adverse effects (Table IV). With use of the life-table method, the overall long-term efficacy rates for sotalol therapy at the 6-, 12- and 18-month follow-up points were 80, 76 and 72%, respectively (Fig. 1). The overall long-term efficacy rates did not differ significantly when expressed as a function of acute-phase response (Fig. 2), although efficacy rates tended to be lower in the nonresponder and nonassessable patient groups (Table V).

Long-term phase mortality: There were 10 deaths during the long-term follow-up phase, 9 of which were sudden and presumably arrhythmic in mechanism, yielding a sudden death incidence of 6%. The remaining death was secondary to progressive cardiac-pump failure.

Arrhythmic recurrence as a function of acute-phase programmed electrical stimulation response: Of the 151 long-term patients, baseline and predischarge PES responses were determined in 68 patients. Thirty-one pa-

TABLE V Long-Term Efficacy of Sotalol as a Percent Function of Acute-Phase Responses

	No. of Pts.	6 Months	12 Months	18 Months	p
Complete responders	63	81	77	77	NS
Partial responder	21	81	81	81	NS
Nonresponder	46	83	75	69	NS
Not assessable	21	71	69	64	NS
Total	151	107 (80)	64 (76)	27 (72)	NS

NS = not significant.

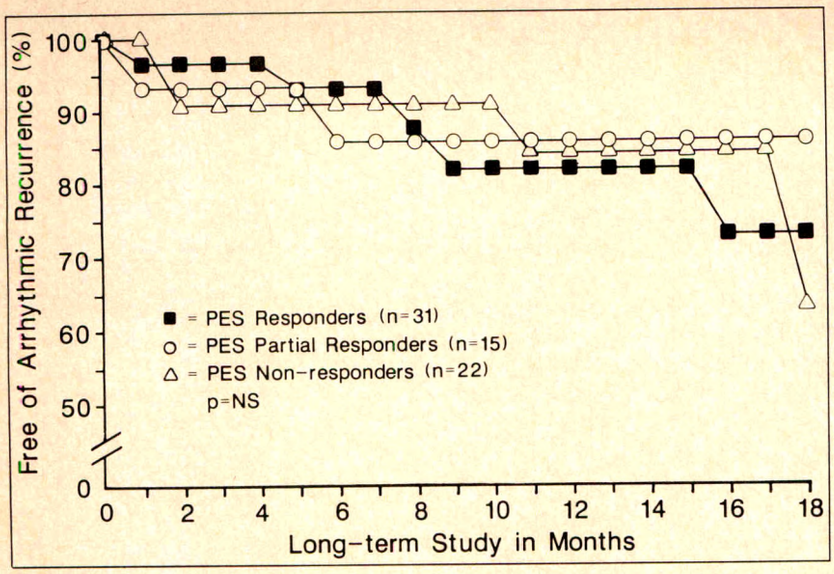


FIGURE 3. Time to arrhythmic recurrence during long-term sotalol therapy as a function of acute phase programmed electrical stimulation (PES) responses in patients with ventricular tachycardia/ventricular fibrillation. Recurrence rates were similar for the 3 groups. NS = not significant.

tients were classified as complete responders, 15 as partial responders and 22 as nonresponders. Nine of these 68 patients (13%) had recurrence of arrhythmia during follow-up. Life-table estimates revealed no significant differences in time to arrhythmic recurrence for the PES complete, partial and nonresponse groups (Fig. 3).

A similar lack of relation between acute-phase response and subsequent arrhythmic recurrence was observed for patients evaluated by either 24-hour ambulatory monitoring or suppression of symptoms methods.

Long-term adverse effects: During the long-term phase, adverse effects serious enough to force discontinuation of sotalol occurred in 10 of the 151 patients (7%). Six patients experienced symptomatic bradycardia, 2 had worsening of congestive heart failure, 1 an exacerbation of obstructive lung disease, and the remaining patient had multiple syncopal episodes secondary to torsades de pointes 3 months after discharge.

DISCUSSION

The objectives of this study were to define the safety and efficacy of oral sotalol in a drug refractory population of patients with sustained VT or VF and, if possible, to determine which arrhythmia assessment technique provided the most useful prognostic information.

Of the 236 patients with sustained VT/VF enrolled in acute-phase therapy, complete response rates ranged from 31 to 51%, depending on the method used to determine efficacy. An additional 12 to 27% of patients exhibited a partial response to sotalol. When PES was used to determine response, 33 of 106 patients (31%) had complete suppression of inducible VT and another 29 (27%) exhibited a strong directional response. When 24-hour ambulatory monitoring served as the arrhythmia assessment technique, the complete and partial response rates were 51 and 12%, respectively. Thus, with application of the 2 most frequently used arrhythmia assessment techniques, sotalol therapy resulted in excellent acute-phase response rates. The finding that 31% of the patients assessed by PES had complete suppression of inducible VT compares quite favorably with the 15 and 12% respective complete-response rates recently reported for encainide and flecainide in similar patient populations.[13,14] This high noninducibility rate in response to sotalol therapy has been observed by several additional investigators who have reported complete or partial response rates to sotalol ranging from 40 to 65%.[7,8,10,11]

During long-term follow-up, sotalol therapy was associated with excellent suppression of recurrent VT/VF in that only 27 patients (18%) sustained arrhythmia recurrence at a mean follow-up of 1 year. After discharge, arrhythmic mortality in this high-risk patient population was only 6%. This low incidence of subsequent sudden death is noteworthy since the index arrhythmia was aborted sudden death in 104 of the 236 patients (44%) enrolled in this study.

Predictors of long-term outcome: In this study, it did not appear that acute-phase responses were helpful in identifying patients likely to sustain arrhythmic recurrence during follow-up. For example, similar recurrence rates were observed for patients who exhibited complete suppression of inducible VT compared with those in whom inducible VT persisted (Fig. 3). A similar lack of predictive utility was noted for patients assessed by the 24-hour ambulatory monitoring method. The inability of acute-phase responses to either PES or 24-hour ambulatory monitoring to predict subsequent outcome may be related in part to the relatively short duration of follow-up, approximately 1 year at the initial reporting of this study. This explanation is supported by the trend for the non-response and empiric therapy groups to have higher recurrence rates, although statistically insignificant when compared with the complete response groups. In addition, the total number of arrhythmic recurrences in the 68 patients assessed by PES was only 9, and thus the lack of a significant difference in outcome may reflect a type II statistical error.

Several other investigators have examined the role of PES responses as predictors of arrhythmia recurrence, and most have found that either a partial or complete

PES response to sotalol was strongly predictive of freedom from arrhythmic recurrence.[8,10,11] In addition, these same investigators found that failure of sotalol therapy to suppress inducible VT was associated with recurrence rates as high as 37%. Although these studies were limited to relatively small numbers, they do suggest that patients in whom sotalol therapy has failed to produce at least a partial response should be considered at enhanced arrhythmic risk and alternative forms of therapy should be pursued. It is hoped that the role of acute-phase PES and 24-hour ambulatory monitoring responses in predicting arrhythmia recurrence will be clarified as enrollment and the length of follow-up increase. Also, data reported here represent an uncontrolled experience at multiple centers; its limitation for formulating valid conclusions regarding the predictive accuracy of PES or ambulatory monitoring for long-term clinical outcome should be recognized.

Overall efficacy: In addition to its ability to suppress the recurrence of symptomatic arrhythmia, another important feature of an antiarrhythmic agent is how well it is tolerated during long-term follow-up. Only 10 of the 151 patients (7%) discharged with sotalol experienced adverse effects serious enough to force discontinuation of therapy. The most common adverse effect encountered was symptomatic bradycardia, which occurred in 6 patients. Interestingly, proarrhythmia (1 patient) and exacerbation of congestive heart failure (1 patient) were uncommon events in the long-term phase. The overall efficacy rates for sotalol therapy in this refractory patient population were 80, 76 and 72% at 6, 12 and 18 months of follow-up, respectively. These overall efficacy rates compare quite favorably with those reported for both amiodarone and the class I antiarrhythmic drugs.[15–17]

Adverse cardiac effects: Proarrhythmic complications documented in 18 of the 236 patients (7%) enrolled in this study were manifested as torsades de pointes in 11 patients and as an increased frequency of sustained VT episodes in 7. This 7% incidence of serious proarrhythmia is similar to the proarrhythmia rates reported for other drugs that have been systematically examined in similar high-risk, drug-refractory patient populations.[13,14,18] All but 1 of these proarrhythmic complications occurred in the acute dose-titration phase, and in 14 patients it was manifested within the first 7 days of therapy. Despite sotalol's β-adrenergic blocking characteristics, the development of symptomatic bradycardia in 8 of the 236 study patients (3%) (7 acute, 1 long-term) and congestive failure in 7 patients (3%) (6 acute, 1 long-term) were relatively uncommon events. The low incidence of congestive failure is noteworthy, since over one-third of the study population had experienced ≥ 1 previous episodes of heart failure and 57% had left ventricular ejection fractions of <40%.

CONCLUSION

This study demonstrates that oral sotalol can provide effective long-term suppression of sustained episodes of VT/VF in patients who have previously experienced drug refractory sustained ventricular tachyarrhythmias. Proarrhythmia was essentially due to the development of torsades de pointes. In most instances, proarrhythmia occurred during the acute dose-titration phase, within 7 days of the initiation of sotalol therapy. Overall, long-term efficacy rates at 12 and 18 months were 76 and 72%, respectively. Long-term tolerance was excellent and withdrawal of therapy for congestive failure or bradyarrhythmia was uncommon. These findings suggest that sotalol will be an important class III β-blocking drug for the therapy of patients with resistant sustained VT or VF.

Acknowledgment: We thank Mary Mays, whose secretarial support was invaluable in the preparation of this manuscript.

REFERENCES

1. Lish PM, Weikel JH, Dungan KW. Pharmacological and toxicological properties of two new beta-adrenergic receptor antagonists. *J Pharmacol Exp Ther 1965;149:161–166.*

2. Singh BN, Vaughan Williams EM. A third class of anti-arrhythmic action: effects on atrial and ventricular intracellular potentials, and other pharmacologic actions on cardiac muscle, of MJ 1999 and AH 3474. *Br J Pharmacol 1970;39:675–682.*

3. Myburgh DP, Goldman AP, Cartoon J, Schamroth JM. The efficacy of sotalol in suppressing ventricular ectopic beats. *Afr Med J 1979;56:295–300.*

4. Singh SN, Cohen A, Chen Y, Wish M, Thoben-O'Grady L, Peralba J, Gottdiener J, Fletcher RD. Sotalol for refractory sustained ventricular tachycardia and nonfatal cardiac arrest. *Am J Cardiol 1988;62:399–402.*

5. Deedwania PC. Suppressant effects of conventional beta-blockers and sotalol on complex and repetitive ventricular premature complexes. *Am J Cardiol 1990;65:43A–50A.*

6. Anderson JL. Effectiveness of sotalol for therapy of complex ventricular arrhythmias and comparisons with placebo and class I antiarrhythmic drugs. *Am J Cardiol 1990;65:37A–42A.*

7. Nademanee K, Feld G, Hendrickson J, Singh PN, Singh BN. Electrophysiologic and anti-arrhythmic effects of sotalol in patients with life-threatening ventricular tachyarrhythmias. *Circulation 1985;72:555–564.*

8. Ruder MA, Ellis T, Lebsack C, Mead RH, Smith NA, Winkle RA. Clinical experience with sotalol in patients with drug-refractory ventricular arrhythmia. *JACC 1989;13:145–152.*

9. Senges J, Lengfelder W, Jauernig R, Czysan E, Brachmann J, Rizos I, Cobbe S, Kubler W. Electrophysiologic testing of therapy with sotalol for sustained ventricular tachycardia. *Circulation 1984;69:577–583.*

10. Gonzalez R, Scheinman MM, Herre JM, Griffin JC, Sauve MJ, Sharkey H. Usefulness of sotalol for drug-refractory malignant ventricular arrhythmias. *JACC 1988;12:1568–1572.*

11. Zheutlin T, Mattioni T, Chokshi S, Nazari J, Dunnington C, Parker M, Nebergall N, Kehoe R. Sotalol for sustained ventricular tachyarrhythmias: predictors of arrhythmic outcome (abstr). *JACC 1988;suppl 1:55A.*

12. Nademanee K, Singh BN. Effects of sotalol on ventricular tachycardia and fibrillation produced by programmed electrical stimulation: comparison with other antiarrhythmic agents. *Am J Cardiol 1990;65:53A–57A.*

13. The Encainide-Ventricular Tachycardia Study Group. Treatment of life-threatening ventricular tachycardia with encainide hydrochloride in patients with left ventricular dysfunction. *Am J Cardiol 1988;62:571–575.*

14. Platia EV, Estes NAM, Heine DL, Griffith LSC, Garan H, Ruskin JN, Reid PR. Flecainide: electrophysiologic and antiarrhythmic properties in refractory ventricular tachycardia. *Am J Cardiol 1985;55:956–962.*

15. Bauman JL, Gallastegui J, Strasberg B, Swiryn S, Hoff J, Welch WJ, Bauernfeind RA. Long-term therapy with disopyramide phosphate: side effects and effectiveness. *Am Heart J 1986;111:654–660.*

16. Denes P, Wu D, Wyndham C, Dhingra R, Bauernfeind R, Swiryn S, Rosen KM. Chronic long-term electrophysiologic study of paroxysmal ventricular tachycardia. *Chest 1980;77:478–483.*

17. Morady F, Sauve MJ, Malone P, Shen EN, Schwartz AB, Bhandari A, Keung E, Sung RJ, Scheinman MM. Long-term efficacy and toxicity of high-dose amiodarone therapy for ventricular tachycardia or ventricular fibrillation. *Am J Cardiol 1983;52:975–979.*

18. Podrid PJ. Aggravation of ventricular arrhythmia. A drug-induced complication. *Drugs 1985;29:suppl 4:33–44.*

APPENDIX

The following group comprised the Sotalol Ventricular Tachycardia Study Investigators: Lapeer County Hospital and Pontiac Osteopathic Hospital, Pontiac, Michigan: Jeffrey Harris, DO; Massachusetts General Hospital, Boston, Massachusetts: Jeremy Ruskin, MD;

Jackson Memorial Hospital, Miami, Florida: Liagat Zaman, MD; University of Louisville School of Medicine, Louisville, Kentucky: Prasad Palakurthy, MD; North East Cardiology Associates, Bangor, Maine: John Jentzer, MD; Wadsworth Veterans Administration Hospital, Los Angeles, California: Bramah N. Singh, MD, and Koonlawee Nademanee, MD; Johns Hopkins Hospital, Baltimore, Maryland: Philip R. Reid, MD, PhD, and Enrico P. Veltri, MD; San Francisco Medical Center, San Francisco, California: Melvin M. Scheinman, MD; Sinai Hospital of Detroit, Detroit, Michigan: Nicholas Z. Kerin, MD; Veterans Administration Medical Center, Washington, D.C.: Steven D. Singh, MD; Northwestern Memorial Hospital, Chicago, Illinois: Richard F. Kehoe, MD; Galichia CV Group, Wichita, Kansas: J. E. Val-Mejias, MD; Medical College of Virginia, Richmond, Virginia: Robert Bauernfeind, MD; Panorama City, California: Carol Zaher, MD; Cedars-Sinai Medical Center, Los Angeles, California: Eli Gang, MD; Sequoia Hospital District, Redwood City, California: Roger A. Winkle, MD; Washington Hospital, Washington, D.C.: Edward V. Platia, MD; Yale-New Haven Hospital, Yale University Medical School, New Haven, Connecticut: Lynda Rosenfeld, MD; Vanderbilt University School of Medicine, Nashville, Tennessee: Raymond L. Woosley, MD, PhD; Daniel Freeman Hospital, Inc., Inglewood, California: March Schwab, MD; Brigham and Women's Hospital, Boston, Massachusetts: Elliot Antman, MD; Oklahoma Memorial Hospital, Oklahoma City, Oklahoma: Karen J. Friday, MD; Montefiore Hospital, Bronx, New York: Soo Kim, MD; Jewish Hospital, St. Louis, Missouri: Rodolphe Ruffy, MD; University of Utah, Salt Lake City, Utah: Roger A. Freedman, MD; Montreal Cardiology Institute, Montreal, Quebec, Canada: Dennis Roy, MD; University of Ottawa Heart Institute, Ottawa Civic Hospital, Ottawa, Ontario, Canada: Martin Green, MD; Vancouver General Hospital, Vancouver, B.C., Canada: Charles R. Kerr, MD.

Discussion III: Effects in Malignant Ventricular Arrhythmias

Dr. Prakash Deedwania (Fresno, California): Dr. Nademanee, I believe that the data you showed on the comparative efficacy of various class IA, IB and IC antiarrhythmics, as well as amiodarone and sotalol, need to be interpreted with a great deal of caution. Is it not so that most of the patients who were studied with type IA and IB agents had already been clinically refractory to these agents before coming to the electrophysiology laboratory? This, I believe, is the usual indication for electrophysiological study; in contrast, those who were studied on sotalol, an investigational agent, were usually participating in a clinical trial and they were not as unstable or as refractory.

Dr. Koonlawee Nademanee (Los Angeles, California): If you are referring to the retrospective data, I agree, as emphasized, that it should be viewed with caution. For this reason, I did not even do a statistical analysis; I was merely illustrating trends. I agree that many patients coming for electrophysiologic testing are selected because they had failed on other drugs previously. They then received investigational therapy, and so it really is not fair to compare different agents in the statistical sense. Interestingly, however, the incidence of success with ventricular tachycardia induction is the same with the controlled multicenter study as it was with our own relatively uncontrolled study; we found that sotalol suppressed induction by 45%. However, in the multicenter study, if you excluded triple-stimuli protocol and used only double stimuli, it was about 52%. This is similar to the results reported by Senges et al[1] in West Germany.

Dr. Deedwania: My second question involves your including patients who had ejection fractions greater than 20% in the multicenter study; you excluded those who had less than a 20% ejection fraction. Do you have any data in those who had ejection fractions between 20 and 30%, and in particular those patients with dilated cardiomyopathy, as to how sotalol fared? I ask because it is known that the β blockers may be beneficial in these patients with dilated cardiomyopathy and left ventricular dysfunction.[2]

Dr. Nademanee: I do, but the numbers are too small. In fact, I had one patient who was receiving the drug; after he had experienced recurrent out-of-hospital cardiac arrest, his ejection fraction was 10%. He subsequently died because of pancreatic cancer.

Dr. Earle Lockhart (New York, New York): Assuming that you have comparable effects based on your data, although it did not look as if sotalol might be better if you had larger numbers, is there any difference in patients who might respond? This was a parallel study, is that correct?

Dr. Nademanee: Yes, it was a parallel study.

Dr. Lockhart: Were any patients crossed over to determine if there was any difference in characteristics between the 2 groups that might enable you to say that 1 regimen might work better than the other?

Dr. Nademanee: There is the so-called "compassionate" protocol, in which failure on procainamide allows the use of sotalol. Dr. Kehoe might comment on this since he summarized that experience.

Question: Regarding your survival and event curves, did you include those continued on sotalol among the nonresponders?

Dr. Richard Kehoe (Chicago, Illinois): Of the nonresponders, approximately one-third were actually continued into the long-term phase. The reasons for that were basically that many of those patients had been multiple-drug failures. There really were no therapeutic alternatives that were considered viable options in the physician's judgment. Of those long-term follow-up patients, about one-third were nonresponders and a somewhat smaller proportion were nonassessable by any technique. However, of the nonresponders, a good fraction of those were still enrolled into the long-term phase of the study. The point is that, in terms of the overall efficacy in the nonresponders and in the nonassessable patients, it looks as if they did not do quite as well as those in whom the electrophysiologic testing was favorable; however, in a formal comparison of the actuarial curves, there was no statistical difference in groups based on response: favorable, unfavorable or not assessable.

Dr. Harold Kennedy (St. Louis, Missouri): I think that in this country we are all agreed that electrophysiologic study is the method of choice for the evaluation of malignant ventricular arrhythmias that are hemodynamically significant. When one presents these data, the only noninvasive data that have stood the test of time in this particular population is the Holter group. Also, in that group, the criteria for Holter efficacy is the elimination of all repetitive activity. It is therefore not surprising that defining a group of patients as having Holter efficacy but still leave repetitive activity will not result in a good outcome. In reporting these data, I must emphasize that one has to use the criteria of a 100% suppression of all repetitive activity. I must also point out that in the Graboys data,[3] it was not just the Holter monitors that were used; exercise testing was also utilized. That study defined efficacy in about 25% more patients by exercise testing. Because we do not have exercise testing here, we might expect that the methodology used was not comprehensive in this group of patients. This may influence assessment of patients. In most protocols, when we examine class IA agents "across the board" in malignant ventricular tachycardia groups, we obtain a group efficacy rate around 30 to 35% in the long term. On this basis, sotalol is very competitive. However, much of the sotalol data being presented is from groups of patients who have a mean failure rate of 5 drugs. From that point of view, then, it

may actually be much better. I also urge you to break down your efficacy rate relative to ejection fraction from 20 to 30%, 30 to 40% and 40 to 50%.

Dr. Kehoe: Your points are all very well stated and well taken. In a multicenter trial with over 20 centers, getting uniform agreement on what criteria for efficacy should be employed, by any method, is obviously difficult, and I think that the reason the data are presented in the format I used is in large measure a function of that difficulty. Therefore, I believe it is a bit unfair to impugn the Holter method, because it really was not applied with great rigor in this study design. I also think your point regarding sotalol being studied in a very resistant patient population is worthy of emphasis.

Dr. Bramah Singh (Los Angeles, California): It has an important bearing on the issue of the intrinsic potency and efficacy of the drug in different subsets of patients with ventricular arrhythmias.

REFERENCES

1. Senges J, Lengfelder W, Jaueonig R, Czygan R, Brachmann J, Rizos I, Cobbe S, Kubler W. Electrophysiologic testing in assessment of therapy with sotalol for sustained ventricular tachycardia. *Circulation 1984;69:577–583.*

2. Hertbrunn SM, Shah P, Bristow R, Valantine HA, Ginsburg R, Fowler MB. Increased beta-receptor density and improved hemodynamic responses to catecholamine stimulation during long-term metoprolol therapy in heart failure from dilated cardiomyopathy. *Circulation 1989;79:483–490.*

3. Graboys TB, Lown B, Podrid PJ, DeSilva R. Long-term survival of patients with malignant ventricular arrhythmia treated with antiarrhythmic drugs. *Am J Cardiol 1982;8:437–443.*

Sotalol for Paroxysmal Supraventricular Tachycardias

A. John Camm, MD, and Vince Paul, BSc, MRCP

Used in adequate dosages, sotalol is efficacious in the conversion of acute supraventricular arrhythmias, an effect that is predictable on the basis of the drug's known electropharmacologic actions. Electrophysiologic studies have shown that both oral and intravenous sotalol are effective in preventing the induction of sustained arrhythmias and that the success of acute suppression is indicative of subsequent clinical control. Interim results of a recent trial of prophylaxis against recurrence of paroxysmal supraventricular tachycardia are reported, demonstrating a high efficacy with an acceptably low profile of adverse effects.

(Am J Cardiol 1990;65:67A–73A)

From the Department of Cardiological Sciences, St. George's Hospital Medical School, London, United Kingdom.

Address for reprints: Professor A. John Camm, MD, Department of Cardiological Sciences, St. George's Hospital Medical School, Cranmaer Terrace, London, SW17 ORE, U.K.

The electrophysiologic profile of sotalol predicts efficacy against supraventricular arrhythmias—paroxysmal supraventricular tachycardia (PSVT) and paroxysmal atrial fibrillation. In 7 open trials, intravenous sotalol (0.4 to 1.5 mg/kg) converted 47 of 106 (46%) episodes of PSVT or paroxysmal atrial fibrillation. In 6 studies, intravenous sotalol (0.6 to 2.75 mg/kg) prevented reinduction of sustained PSVT in 44 of 74 patients (59%). Oral sotalol prevented restimulation of PSVT in 19 of 28 patients (68%) (3 trials). In 1 study, sotalol was more effective than metoprolol in preventing reinduction of PSVT (59 vs 28%, $p < 0.05$).

In a variety of open clinical studies involving 74 patients with resistant PSVT, sotalol achieved complete or partial suppression in 39% of patients. Sotalol (160 to 320 mg administered twice daily) and quinidine (200 to 400 mg administered 4 times daily) showed similar efficacy (53 vs 48%, respectively) in the maintenance of sinus rhythm in 183 patients after electrocardioversion. Postoperative supraventricular arrhythmias in 161 patients were reduced from 37% (with placebo) to 2% (with sotalol). In a crossover comparison, sotalol was more successful (62%) than atenolol (31%) in preventing clinical recurrences of PSVT in 13 patients.

A parallel-design (3-limb), multicenter, double-blind, placebo-controlled trial of sotalol (80 and 160 mg given twice daily) enrolled 64 patients, of whom 58 were assessed for primary efficacy and 39 completed the double-blind period. Trial entry required that the patient must have had at least 1 attack of tachycardia during each of 3 consecutive baseline assessment periods (1 to 4 weeks). The treatment phase lasted 2 baseline periods or until a single paroxysm occurred. There were 20 of 21 recurrences (95%) in the placebo group compared with 11 of 16 (69%) in those receiving sotalol, 80 mg twice daily and 12 of 21 (57%) receiving sotalol, 160 mg twice daily ($p = 0.54$ and 0.012, respectively). The relative risks of recurrence (vs placebo) were 0.61 for sotalol, 80 mg twice daily ($p = 0.194$), and 0.41 for sotalol, 160 mg twice daily ($p = 0.022$). Apart from QT-interval prolongation, adverse effects were few and arrhythmogenic effects did not occur.

Electrophysiologic studies and clinical experience attest to the value (high efficacy and low incidence of adverse effects) of both intravenous and oral sotalol for the treatment of paroxysmal supraventricular arrhythmias.

SOTALOL IN THE MANAGEMENT OF SUPRAVENTRICULAR ARRHYTHMIAS

Initially introduced for treatment of angina and hypertension, sotalol is a nonselective β blocker that is de-

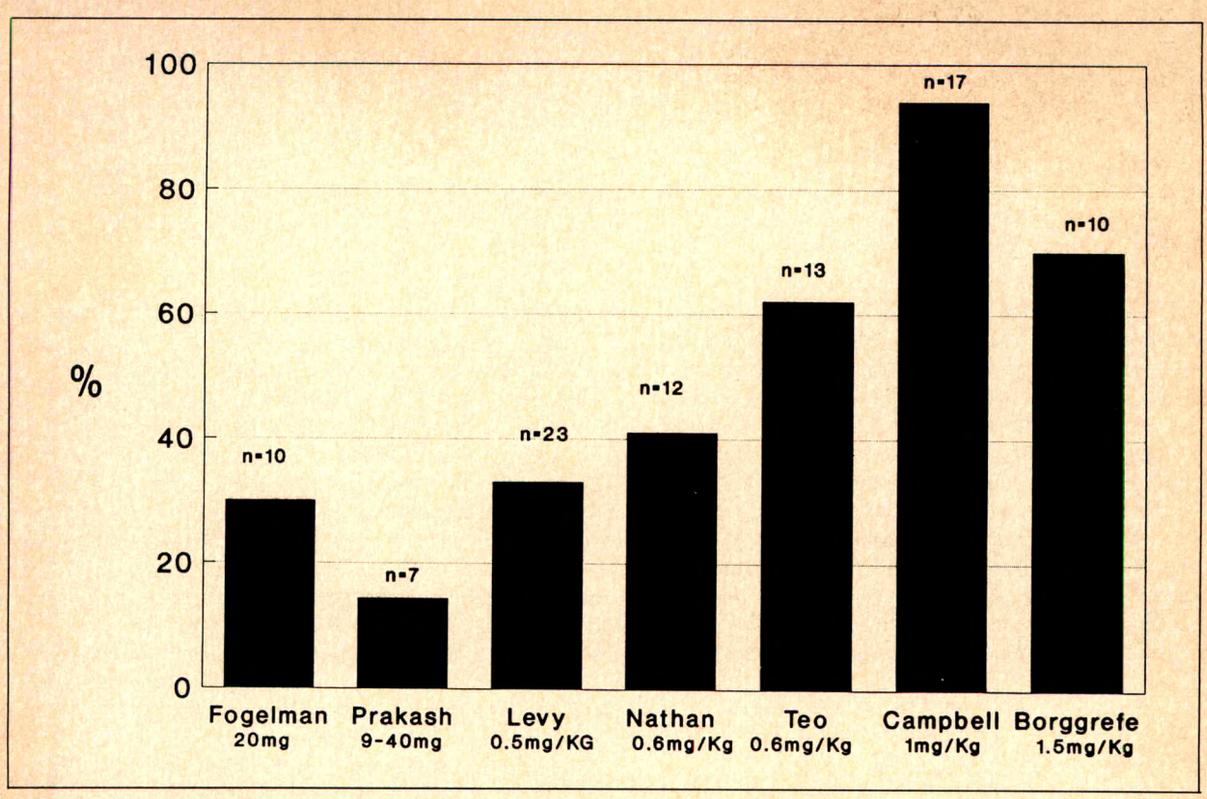


FIGURE 1. Efficacy of intravenous sotalol in the acute conversion of paroxysmal supraventricular tachycardia.

void of intrinsic sympathomimetic and membrane-stabilizing activity. Both Singh and Vaughn Williams[1] and Strauss et al[2] demonstrated that sotalol possesses electrophysiologic effects exceeding those of conventional β blockers. Sotalol, in addition to slowing sinus rate and depressing atrioventricular (AV) nodal conduction, produces an increase in the duration of the action potential with lengthening of the effective and absolute refractory periods.

These changes are present in accessory pathways in addition to atrial and ventricular tissue,[3,4] suggesting widespread antiarrhythmic efficacy particularly in reentrant tachycardias. Similarly, the homogeneous increase in the refractory period of the atrium[5] should help in the treatment of atrial fibrillation and flutter.

Previous studies of sotalol in the control of supraventricular arrhythmias: Although intravenous administration of sotalol rapidly achieves therapeutic plasma levels with associated electrophysiologic effects, early studies of acute termination were disappointing. Fogelman et al[6] reverted acute-onset atrial fibrillation in 3 of 5 patients with a single bolus but failed to terminate 5 cases of atrial flutter. Prakash et al[7] combined a single intravenous bolus with subsequent oral dosing administered every 6 hours but failed to convert 3 cases of atrial fibrillation and was successful in only 1 of 4 cases of atrial flutter. A single bolus of 0.5 mg/kg of sotalol produced sinus rhythm in 4 of 13 patients with atrial flutter/fibrillation and in 3 of 10 patients with junctional arrhythmias.[8] A similar dosage (0.4 mg/kg) administered during AV reentrant tachycardia by Nathan et al[9] to 12 patients with Wolff-Parkinson-White (WPW) syndrome achieved reversion in only 5 patients, although the tachycardia was significantly decreased in the rest. Both the anterograde and retrograde refractory periods of the accessory pathways were increased but most tachycardias terminated in the anterograde limb, suggesting a predominantly AV nodal effect.

The low success rates achieved in the aforementioned studies may be a reflection of the dosages used. Fogelman gave only 20 mg, whereas Prakash administered between 9 and 40 mg. The current dosage recommended, 1.5 mg/kg, gives an improved success rate in a variety of arrhythmias (Fig. 1).

Borggrefe and Breithardt[10] demonstrated reversion of AV reentrant tachycardia in 7 of 10 patients with WPW syndrome using this dosage; block occurred in the AV node in 5 patients and in the retrograde limb in 2 patients. Waleffe et al[11] achieved reversion in 7 of 10 patients with either AV nodal reentrant tachycardia or AV reentrant tachycardia, again using 1.5 mg/kg.

Higher dosages (2 mg/kg) of both d- and dl-sotalol are also associated with an improved success rate in the conversion of experimentally induced canine atrial flutter, although human experience is lacking. Feld et al[12] produced reversion in 14 of 15 patients with atrial flutter with a bolus dose of 2 mg/kg, whereas Okumura et al[13] achieved reversion in 6 of 7 patients with d-sotalol (mean time 4 minutes 37 seconds) and in 8 of 8 patients with dl-sotalol (mean time 2 minutes 15 seconds).

The form of administration may also influence efficacy, since Teo et al[14] showed an infusion of sotalol to be

superior to a single bolus. An infusion produced reversion in 6 of 7 patients with atrial flutter and in 2 of 6 patients with atrial fibrillation, whereas a single bolus dose achieved reversion in 2 of 6 and 1 of 5 patients, respectively.

The influence of intravenous (Table I) and oral sotalol on the inducibility of arrhythmias has been extensively studied in recent years and is generally comparable. In keeping with its major site of action (the AV node), sotalol tends to be more effective in the supression of AV nodal reentrant tachycardia than in AV reentrant tachycardia and more effective in reentrant junctional arrhythmias than in paroxysmal atrial flutter or fibrillation. Noninducibility predicts subsequent clinical success, although inducibility does not necessarily indicate failure.

Manz et al[15] found that an 80-mg bolus dose of sotalol suppressed induction in 6 of 18 patients with WPW syndrome or AV reentrant tachycardia, whereas Touboul et al[4] achieved noninducibility after administration of 0.6 mg/kg sotalol in 5 of 9 patients with WPW syndrome. Suppression of the arrhythmia was largely in the AV node, and although the retrograde effective refractory period of the accessory pathway was uniformly increased, the effect on the anterograde refractory period of the accessory pathway was variable in the latter study. Using a high dosage (1.5 mg/kg), Rizos et al[16] attained noninducibility in 6 of 8 patients with AV nodal reentrant tachycardia and in 4 of 9 patients with AV reentrant tachycardia, whereas Borggrefe rendered the tachycardia noninducible in 5 and nonsustained in 4 of 12 patients with WPW syndrome. Sahar et al[17] recently investigated the effect of d-sotalol on a variety of supraventricular arrhythmias. After administering a bolus of 1.5 to 2.75 mg, noninducibility was unsuccessful in 3 of 4 patients with PSVT and in 1 of 2 with paroxysmal atrial fibrillation, whereas persistent junctional tachycardia was terminated in 1 patient and atrial flutter was decreased in another patient. Of these 10 patients, 9 had improvement with oral d-sotalol, but exact rates of recurrence were not given.

Much of the published data on the prophylactic value of sotalol in the management of supraventricular tachycardias has been derived from studies[17–20] in which the patients have been maintained with the oral preparation after undergoing acute electrophysiologic testing. Although this approach may result in a biased population being followed, it also provides valuable information on the predictive value of testing. The prevention of induction and the restriction to a nonsustained tachycardia were both considered by Kunze et al[18] to be predictive of subsequent clinical outcome. In 17 patients with WPW syndrome, the arrhythmia was inducible in 15 at baseline and in 14 after an intravenous bolus of 1.5 mg/kg of sotalol, but in 10 of these the tachycardia was unsustained. In 7 of the patients who underwent repeat electrophysiologic testing after oral administration of sotalol, the results were similar. Of these patients, 16 were maintained with oral sotalol, and during follow-up (median 36 months) 9 were free from recurrence, whereas 6 had a reduction in their symptoms. Programmed electrical stimulation predicted clinical outcome in 63% after intravenous and in 86% after oral sotalol. In 11 patients with WPW syndrome, Mitchell et al[19] considered a successful result of oral sotalol to be a reduction in the inducibility of tachycardias and an increase in the minimum RR interval during atrial fibrillation to greater than 300 ms. Eight patients fulfilled these criteria: noninducibility in 4 and nonsustained in the remaining 4. During subsequent follow-up (15 ± 12 months) with oral sotalol no patient had a recurrence of their arrhythmia. In 10 patients with AV reentrant tachycardia and AV nodal reentrant tachycardia, Cassidy et al[20] found noninducibility in 7 after ad-

TABLE I Efficacy of Intravenous Sotalol in the Prevention of Sustained Arrhythmia Induction

Investigator	Arrhythmia	Dosage	Efficacy
Manz[15]	AVRT-WPW	80 mg	6/18
Touboul[4]	WPW	0.6 mg/kg	5/9
Rizos[16]	AVNRT	1.5 mg/kg	6/8
	AVRT		4/9
Borggrefe[10]	AVRT	1.5 mg/kg	9/12
Kunze[18]	AVRT	1.5 mg/kg	11/14

AVRT = atrioventricular reentrant tachycardia; WPW = Wolff-Parkinson-White.

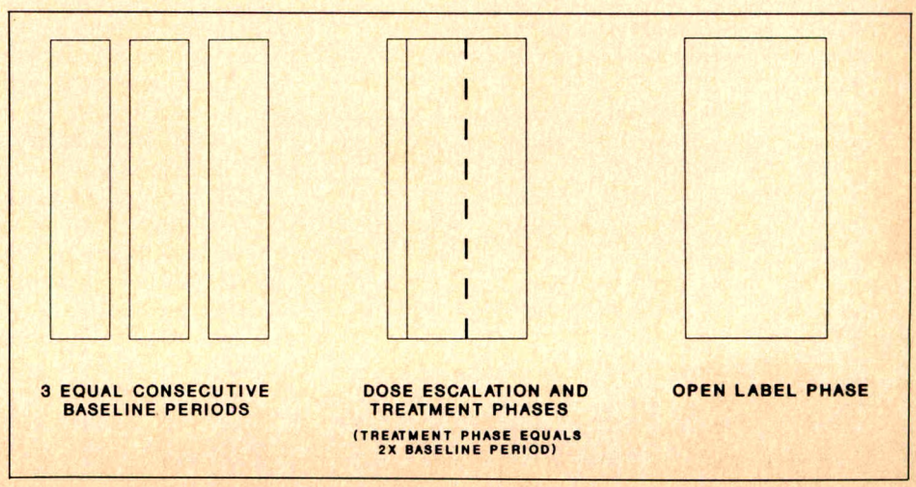


FIGURE 2. Trial design for the paroxysmal supraventricular tachycardia study.

TABLE II Patient Characteristics in the Sotalol Paroxysmal Supraventricular Tachycardia Study

Characteristics	Placebo (n = 22)	Sotalol 80 mg b.i.d. (n = 20)	Sotalol 160 mg b.i.d. (n = 22)
Gender (M/F)	10/12	14/6	13/9
Age (yrs), mean/median	48/50	57/59	54/56
Weight (kg), mean/median	76.2/74	77.7/79.1	76/78.1
Heart rate (beats/min), mean/median	76/75	77/73	74/70
Systolic BP (mm Hg), mean/median	135/130	141/140	138/133
Diastolic BP (mm Hg), mean/median	79/80	85/83	84/85

b.i.d. = twice daily; BP = blood pressure.

TABLE III Diagnoses of Supraventricular Tachyarrhythmias in the Sotalol Paroxysmal Supraventricular Tachycardia Study

Type of Supraventricular Arrhythmia	Number of Patients (%)		
		Sotalol	
	Placebo (n = 22)	80 mg b.i.d. (n = 20)	160 mg b.i.d. (n = 22)
Sinus tachycardia	2 (9)	0	0
Atrial fibrillation	9 (41)	10 (50)	12 (55)
Atrial flutter	1 (5)	3 (15)	1 (5)
Atrial tachycardia	6 (27)	7 (35)	3 (14)
AV nodal reentrant tachycardia	3 (14)	1 (5)	3 (14)
Junctional tachycardia	3 (14)	3 (15)	1 (5)
Atrial ectopic beat	1 (5)	0	0
WPW syndrome	1 (5)	0	4 (18)
Atrial fibrillation	1 (5)	0	0
PSVT	1 (5)	0	3 (14)
Concealed	0	0	2 (9)
Lown-Ganong-Levine syndrome	1 (5)	0	0
Other	1 (5)	0	0

AV = atrioventricular; b.i.d. = twice daily; PSVT = paroxysmal supraventricular tachycardia; WPW = Wolff-Parkinson-White.

TABLE IV History of Supraventricular Tachyarrhythmias in the Sotalol Paroxysmal Supraventricular Tachycardia Study

Variable	Placebo	Sotalol 80 mg b.i.d.	Sotalol 160 mg b.i.d.
Arrhythmia duration			
No. of pts.	22	17	21
Mean/median	6.8/4.5	8.7/6.0	9.3/4.5
Arrhythmia frequency			
No. of pts.	21	20	22
Number/month (mean/median)	14.2/6.0	7.0/4.0	5.7/3.5
Tachycardia rate			
No. of pts.	18	16	18
Mean/median (beats/min)	161/150	158/150	154/150

ministration of oral sotalol (80 to 480 mg/day). During a limited follow-up (5 ± 4 months), 3 of these remained free from recurrence, whereas 3 had a marked reduction in the frequency of attacks.

DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF SOTALOL IN THE PROPHYLAXIS OF PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIAS

A placebo-controlled, randomized, double-blind, multicenter trial has recently been designed to determine the efficacy of oral sotalol in the prophylaxis of a variety of supraventricular arrhythmias. Unlike previous studies, it assesses the effects of sotalol in patients with frequent (>1 attack per month) symptomatic palpitations without prior acute testing. Patients aged 18 to 80 years with evidence of arrhythmia (on electrocardiography or Holter monitoring) during a symptomatic episode were eligible for inclusion provided they had not been totally refractory to previous antiarrhythmic medication.

The novel study design (Fig. 2) overcomes some of the difficulties encountered in assessing the control of a variable and episodic condition. The duration of the study period was determined by the frequency of episodes during 3 baseline off-therapy periods of variable duration (1 to 4 weeks). The double-blind phase consisted of an initial 1-week dose escalation period during which patients received either a placebo or sotalol, 80 mg twice daily. This was followed by 2 periods of equal duration to the baseline phase, during which patients continued to take either placebo or sotalol in dosages of either 80 or 160 mg twice daily. The efficacy of the treatment was assessed in terms of relative risk and the time to first recurrence.

The planned enrollment of 125 patients has now been achieved, and results are available for 64 patients who have completed the trial. Patient characteristics, underlying arrhythmia, prior medication and history of attacks are listed in Tables II to VI.

Of the patients randomized to receive 160 mg of sotalol twice daily, 45% were free from tachycardia recurrence during the treatment phase, a significant improvement in the 5% freedom from relapse recorded in the placebo group. Sotalol, 80 mg twice daily, showed a trend toward successful control but did not quite reach statistical significance, with 31% of patients free from relapse during the treatment period (Fig. 3). Investigators classified patient response to treatment as completely or partially successful in 62% of patients taking 160 mg twice daily, in 50% taking 80 mg twice daily, and in 3% taking placebo. Patients with a variety of arrhythmias have been enrolled in this study, and although numbers do not yet allow statistical analysis, it would appear that greater success is achieved in the management of reentrant tachycardias than in paroxysmal atrial fibrillation (Fig. 4). Only 16% of patients with paroxysmal atrial fibrillation remained free from tachycardia during the double-blind phase compared with 61% of patients with other forms of PSVT.

The incidence of adverse effects has been acceptably low (Table VI); only 2 patients (1 from each sotalol

TABLE V Number (%) of Patients Who Received Prior Antiarrhythmic Medication in the Sotalol Paroxysmal Supraventricular Tachycardia Study

Class of Antiarrhythmic Medication	Placebo (n = 22)	Sotalol 80 mg b.i.d. (n = 20)	Sotalol 160 mg b.i.d. (n = 22)
Any antiarrhythmic	11 (50)	12 (60)	17 (77)
IA	5 (23)	5 (25)	6 (28)
IB	1 (5)	0	0
IC	3 (14)	1 (5)	5 (23)
II	6 (27)	5 (25)	11 (50)
III	2 (9)	2 (10)	3 (14)
IV	3 (14)	3 (15)	7 (32)
Cardiac glycosides	8 (36)	9 (45)	8 (36)
Unclassified	0	1 (5)	0

b.i.d. = twice daily.

TABLE VI History of Attacks

Adverse Effect	Placebo (n = 22)	Sotalol 80 mg b.i.d. (n = 20)	Sotalol 160 mg b.i.d. (n = 22)
Proarrhythmia	0	0	0
Bradycardia	0	1	1
GI tract disturbance	0	1	0
Weight change	0	0	1
Musculoskeletal	1	0	1
Fatigue	0	2	4
Asthenia	0	5	6
Headache	2	1	0
Respiratory	1	0	2
Total	4	6	8

b.i.d. = twice daily; GI = gastrointestinal.

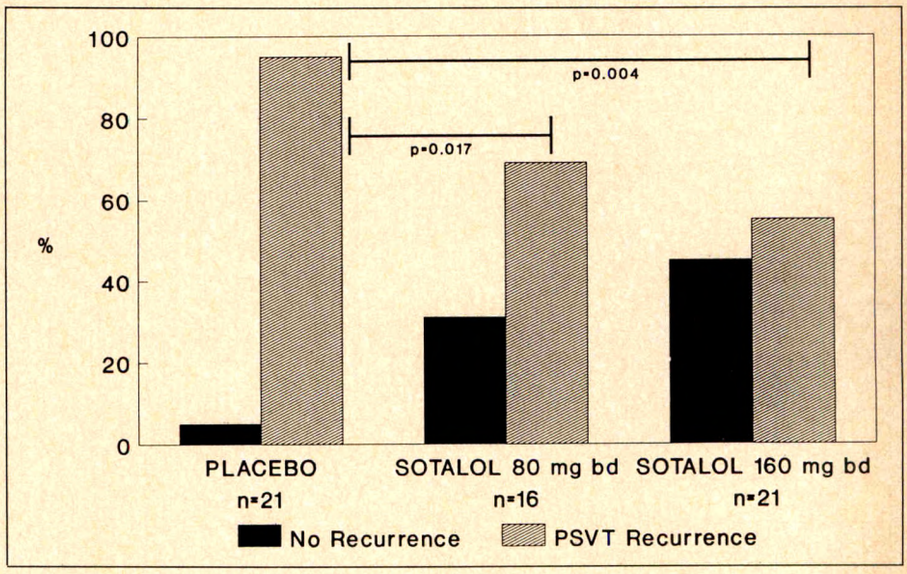


FIGURE 3. Summary of efficacy of intent to treat in the sotalol paroxysmal supraventricular tachycardia (PSVT) study.

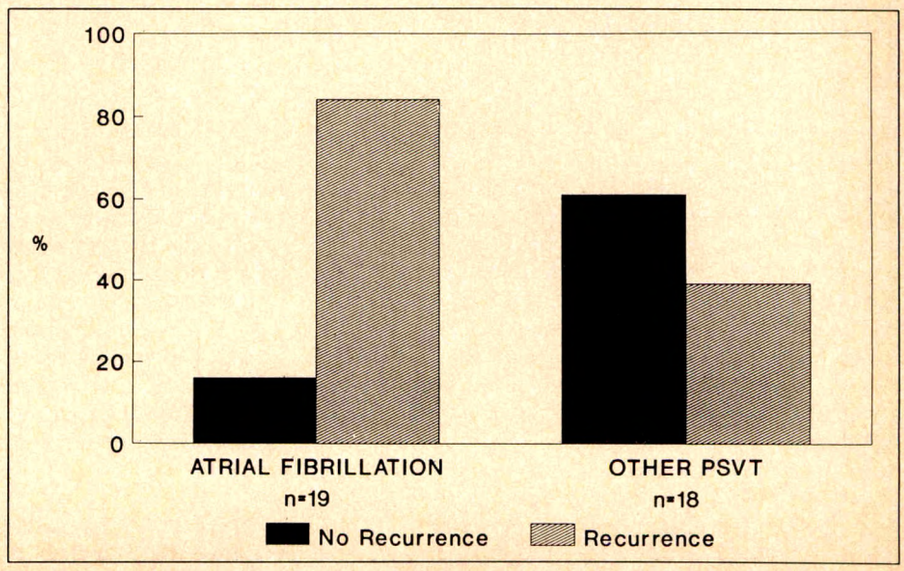


FIGURE 4. Comparison of response: paroxysmal atrial fibrillation vs other paroxysmal supraventricular tachycardia (PSVT) in the sotalol PSVT study.

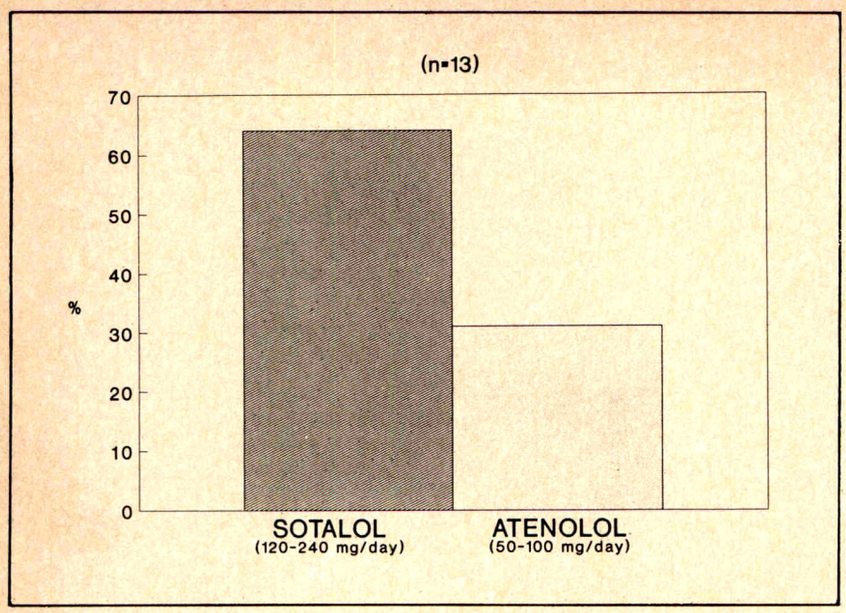


FIGURE 5. Crossover comparison of sotalol vs atenolol, freedom from relapse at 6 weeks.

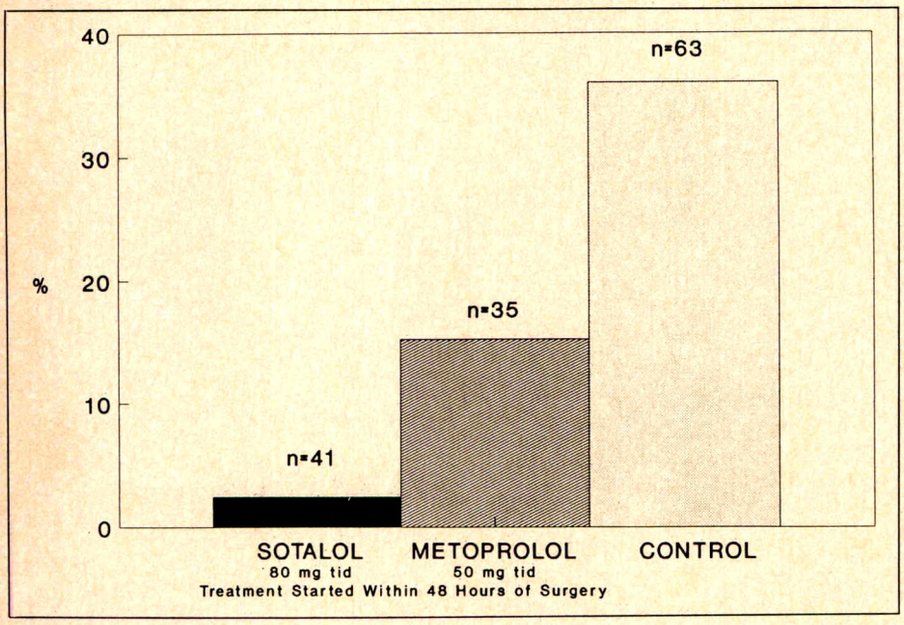


FIGURE 6. Incidence of supraventricular arrhythmia after coronary artery bypass graft surgery (randomized open trial).

group) withdrew. Significant prolongation of the QT interval, compared with baseline, was observed in both groups receiving sotalol (mean increase 47 ± 14 ms for sotalol, 80 mg twice daily, and 58 ± 12 ms for sotalol, 160 mg twice daily). However, the changes were largely rate-related and the increases in QTc were not significant (3 ± 9 and 7 ± 9 ms). There was no lengthening of the QTc beyond 550 ms, and no proarrhythmic effects were observed. The precise incidence of proarrhythmic effects due to sotalol is unknown, but reported cases are infrequent. Torsades de pointes is more likely to occur in the presence of supratherapeutic plasma levels caused by overdosage or renal failure or in the presence of electrolyte disturbance.

The most adverse effects could be attributed to the β-blocking properties of sotalol, with fatigue or asthenia being the predominant complaint. However, as with other hydrophilic β blockers, the incidence of central nervous system side effects was low. Sotalol (possibly due to an increase in the duration of the action potential) may have less propensity than other β blockers to aggravate cardiac failure. In the trial, no deterioration of cardiac function occurred, although patients with New York Heart Association class IV heart failure were excluded. In the dosages used, there have been few respiratory problems but patients with contraindications to β blockade were excluded.

EFFICACY OF SOTALOL COMPARED WITH OTHER ANTIARRHYTHMIC DRUGS

Generally, sotalol appears to be better tolerated than other antiarrhythmic agents and equally as effective. In

an open, active-controlled trial of 183 patients, the safety and efficacy of sotalol has been compared with quinidine in its ability to maintain sinus rhythm after direct-current conversion of atrial fibrillation. Although efficacy of the drugs was similar (53% of those taking sotalol were still in sinus rhythm 6 months after shock compared with 48% of those treated with quinidine), sotalol was better tolerated by the patients. Atrial fibrillation in these cases was generally of short duration (75% in less than 6 months) before conversion. A small active-controlled, double-blind, crossover evaluation[21] showed sotalol (120 to 240 mg/day) to be significantly more effective and better tolerated in the prophylaxis against PSVT than atenolol (50 to 100 mg/day) (Fig. 5). However, in a large, multicenter, open, historically controlled trial of 74 patients, who had been inadequately controlled with other antiarrhythmic drugs, sotalol produced complete or partial suppression in 39%.

Sotalol has also demonstrated greater success than other antiarrhythmic drugs in the control of postoperative arrhythmias. Campbell et al[22] compared sotalol (given as an initial bolus of 1.0 mg/kg, followed by an infusion of 0.2 mg/kg/hour) with a digoxin/disopyramide combination. Although both regimens achieved a reversion rate of 17 of 20 in 24 hours, reversion was significantly more rapid in the sotalol group. In a randomized trial of 161 patients, Janssen et al[23] demonstrated sotalol to be superior to both placebo and metoprolol in the prophylaxis of postoperative arrhythmias (Fig. 6) and to achieve reversion more rapidly when tachycardias occurred.

Patients treated prophylactically received either sotalol as an intravenous bolus of 0.3 mg/kg within 1 hour of operation followed by 80 mg 3 times daily at 24 hours, or intravenous metoprolol, 0.1 mg/kg, followed at 24 hours by 50 mg twice daily. In the placebo group, there was a 36% incidence of supraventricular tachycardia postoperatively compared with 15.2% in the group receiving metoprolol and 2.4% in those receiving sotalol.

CONCLUSION

Used in adequate dosages, sotalol is efficacious in the conversion of acute supraventricular arrhythmias. Electrophysiologic studies have shown that both oral and intravenous sotalol are effective in preventing the induction of sustained arrhythmias and that the success of acute suppression is indicative of subsequent clinical control. Trials of prophylaxis demonstrate a high efficacy with an acceptably low profile of adverse effects, confirming the value of sotalol in the management of supraventricular tachycardias.

REFERENCES

1. Singh BN, Vaughn Williams EM. A third class of antiarrhythmic action: effects on atrial and ventricular intracellular potentials, and other pharmacological actions on cardiac muscle of MJ 1999 and AH 3474. *Br J Pharmacol 1970;39:675–689.*

2. Strauss HC, Bigger JT, Hoffman BF. Electrophysiological and beta-receptor blocking effects of MJ 1999 on dog and rabbit cardiac tissue. *Circ Res 1970;26:661–670.*

3. Blanc JJ, Boschat J, Ollivier JP, Penther PH. Effects of oral sotalol on the conduction of accessory atrioventricular pathways. *Arch Mal Coeur 1985;78: 1097–1102.*

4. Touboul P, Atallah G, Kirkorian G, Lavaud P, Matthieu M, Dellinger A. Effects of intravenous sotalol in patients with atrioventricular accessory pathways. *Am Heart J 1987;114:545–550.*

5. Hayward RP, Taggart P. Effect of sotalol on human atrial action potential duration and refractoriness: cycle length dependency of class III activity. *Circ Res 1986;20:100–107.*

6. Fogelman F, Lightman SL, Sillet RW, McNicoll MW. The treatment of cardiac arrhythmias with sotalol. *Eur J Clin Pharmacol 1972;5:72–76.*

7. Prakash R, Parmley WW, Allen HN, Matloff JM. Effect of sotalol on clinical arrhythmias. *Am J Cardiol 1972;29:397–400.*

8. Levy S, Rovini JC, Metge M, Cointe R, Bru P, Nassi C, Gerard R. Intravenous sotalol in the acute treatment of supraventricular tachyarrhythmias. *Arch Mal Coeur 1986;79:1781–1785.*

9. Nathan AW, Hellestrand KJ, Bexton RS, Spurell RA, Camm AJ. Electrophysiological effects of sotalol—just another beta blocker? *Br Heart J 1982; 47:515–520.*

10. Borggrefe M, Breithardt G. Electrophysiologic effect of sotalol in supraventricular tachycardias. *Z Kardiol 1985;74:506–511.*

11. Waleffe A, Hastir F, Kulbertus H. Mechanisms of termination of supraventricular tachycardias by class III agents: a comparison of amiodarone and sotalol (abstr). *Proc Int Symp on Cardiovascular Pharmacology, Geneva, 1985.*

12. Feld GK, Ventkash N, Singh BN. Pharmacologic conversion and suppression of experimental canine atrial flutter: differing effects of d-sotalol, quinidine and lidocaine and significance of changes in refractoriness and conduction. *Circulation 1986;74:197–204.*

13. Okumura K, Scalabrini A, Waldo AL. Effects of d- and l-sotalol on atrial electrophysiology and atrial flutter induced in conscious dogs with sterile pericarditis (abstr). *JACC 1986;7:250A.*

14. Teo KK, Harte M, Horgan JH. Sotalol infusion in the treatment of supraventricular tachyarrhythmias. *Chest 1985;87:113–118.*

15. Manz M, Kuhl AJ, Luderitz B. Sotalol in supraventricular tachycardia. Electrophysiologic measurements in Wolff-Parkinson-White syndrome and AV nodal re-entry tachycardia. *Z Kardiol 1985;74:500–565.*

16. Rizos I, Senges J, Jauernig R, Lendfelder W, Czygane E, Brachmann J, Kubler W. Differential effects of sotalol and metoprolol on induction of paroxysmal supraventricular tachycardia. *Am J Cardiol 1984;53:1022–1027.*

17. Sahar DI, Reiffel JA, Bigger JT, Kidwell GA, Squatrito AM. Efficacy, safety and tolerance of d-sotalol in patients with refractory supraventricular tachyarrhythmias (abstr). *Circulation 1987;76:IV–368.*

18. Kunze KP, Schulter M, Kuck KH. Sotalol in patients with Wolff-Parkinson-White syndrome. *Circulation 1987;76:1050–1057.*

19. Mitchell LB, Wyse G, Duff HJ. Electropharmacology of sotalol in patients with Wolff-Parkinson-White syndrome. *Circulation 1987;76:810–818.*

20. Cassidy DM, Arenal A, Roy D. Oral sotalol: electrophysiological effects and long term efficacy in patients with recurrent supraventricular tachycardia (abstr). *JACC 1987;9:49A.*

21. Schofield PM, Bennett DH. A comparison of atenolol and sotalol in the treatment of patients with paroxysmal supraventricular tachycardia (abstr). *JACC 1987;9:247A.*

22. Campbell TJ, Gavaghan TP, Morgan JJ. Intravenous sotalol for the treatment of atrial fibrillation and flutter after cardiopulmonary bypass. *Br Heart J 1985;54:86–90.*

23. Janssen J, Loomans L, Harink J, Taams M, Brunninkhuis L, Van der Starre P, Kootstra G. Prevention and treatment of supraventricular tachycardia shortly after coronary bypass grafting: a randomized open trial. *Angiology 1985;36:601–604.*

APPENDIX

Investigators involved in paroxysmal supraventricular tachycardia trial: K. Anderson, Utah; D. Bennett, Manchester; A. J. Camm, London; S. Cobbe, Glasgow; J. C. Fofar, Oxford; A. M. Harris, London; K. Jennings, Aberdeen; S. P. Joseph, London; M. Joy, London; T. Moccetti, Lugano; J. E. F. Pohl, Leicester; J. E. Sanderson, Taunton; J. Thirkettle, London.

Clinical Safety Profile of Sotalol in Patients with Arrhythmias

Lester F. Soyka, MD, Carol Wirtz, RN, MSN, and Robert B. Spangenberg MD, PhD

Key safety parameters of sotalol were examined in 1,288 patients entered into recent controlled trials of ventricular (85% of patients) or supraventricular arrhythmias (15%). Most patients were middle-aged male Caucasians with significant heart disease.

The most serious adverse event was proarrhythmia, occurring in 56 patients (4.3%). Of these, 27 had hemodynamic compromise due to malignant ventricular arrhythmias. Most had a history of sustained ventricular tachycardia, myocardial infarction, congestive heart failure (CHF) or cardiomyopathy, or a combination of these. The other 29 had nonsevere events; 38% continued taking sotalol. Proarrhythmia was manifested by torsades de pointes in 24 of the 56 patients. No universal causal relation was found with commonly associated factors such as bradycardia, hypokalemia and long QT interval. The mean QT and QTc at baseline within 1 week of a severe proarrhythmic event were greater than those of patients not having proarrhythmia.

Nineteen patients (1%) discontinued therapy with sotalol because of drug-related CHF. Predisposing conditions included low initial baseline ejection fraction, history of CHF, cardiomyopathy or cardiomegaly, or both, male gender and age >65 years. Heart failure usually occurred within 7 to 30 days of initiating therapy.

The most common reason for premature discontinuation of the drug in patients treated for sustained ventricular tachycardia was ineffectiveness (39%), whereas adverse effects were the most common reasons among patients treated for complex ventricular ectopy (21%). Dyspnea and bradycardia were the most common cardiovascular effects, and fatigue, dizziness and asthenia the most common noncardiac, adverse effects. Although frequently reported, these adverse effects resulted in discontinuation of only 1 to 4% of the patients at risk.

Considering the benefits of the antiarrhythmic and β-blocking effects of sotalol, its risk/benefit ratio is highly favorable for the treatment of ventricular and supraventricular arrhythmias.

(Am J Cardiol 1990;65:74A–81A)

From the Cardiovascular Clinical Research, Bristol-Myers Squibb Company, Wallingford, Connecticut.

Address for reprints: Lester F. Soyka, MD, Bristol-Myers Squibb Company, 5 Research Parkway, P.O. Box 5100, Wallingford, Connecticut 06492.

Sotalol hydrochloride was synthesized in 1960 by Mead Johnson Laboratories and characterized in 1965 as a β blocker.[1] Marketed in Europe, Canada, Australia, South Africa and elsewhere since 1974, its use has been primarily for treatment of hypertension, angina pectoris and arrhythmias. The ability of sotalol hydrochloride to prolong the action potential duration of myocardial fibers was recognized as early as 1968.[2] Definitive studies by Singh and Vaughan Williams[3] provided a new category in the classification of the electrophysiologic characteristics of antiarrhythmic drugs, namely, class III. Recently, interest in the therapeutic usefulness of an agent possessing both β-blocking (class II) and class III properties has resulted in a rapid expansion of studies in patients with ventricular and supraventricular arrhythmias, with particular emphasis on life-threatening ventricular arrhythmias. Comprehensive reviews have appeared.[4,5]

Trials were sponsored by Bristol-Myers Company to provide a basis for a New Drug Application seeking approval for marketing of sotalol hydrochloride in the United States. These controlled trials, plus data derived from supportive and retrospectively collected data from arrhythmia studies performed in Europe and the Republic of South Africa, provide the foundation for evaluating the safety of sotalol. In addition, a large data base derived from more than a decade of clinical trials in the treatment of hypertension, angina pectoris, and secondary prevention in patients with myocardial infarction, plus postmarketing and medical reports, have been examined, but an analysis is beyond the scope of this article.

This review will focus on the safety aspects of the arrhythmia studies, with emphasis on controlled trials.

METHODS

Data base: The data were derived from 181 clinical studies that enrolled 5,856 patients or subjects. The most important single group of these studies consists of 12 randomized, double-blind, placebo-, active drug- or historic-controlled trials that enrolled 1,288 patients. These data were placed in a composite electronic data base, termed the current controlled arrhythmia trials, and provide the best single source for documenting safety. In addition, there were (1) 3 other controlled arrhythmia trials with 136 patients that, because of their design, could not be appropriately merged with the first group; (2) 6 supportive trials with 147 patients; and (3) 5 studies enrolling 454 patients conducted in a retrospective manner. For the latter, data were collected on Bristol-Myers' designed case report forms from trials conducted by leading investigators in Europe and South Africa. The balance of the data base, i.e., 155 studies enrolling 3,831

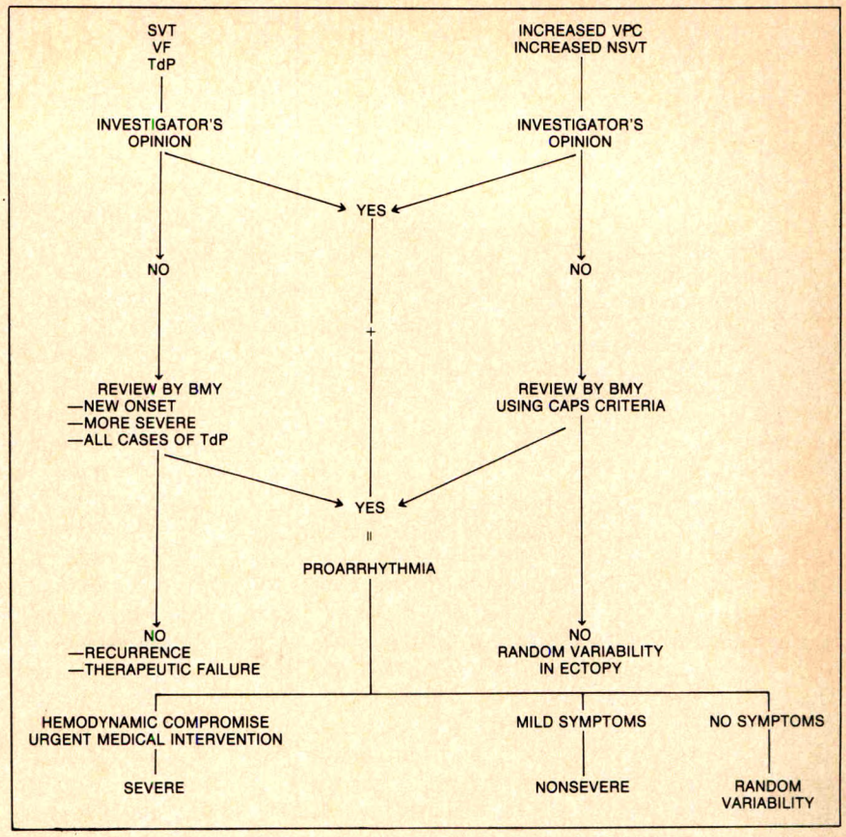


FIGURE 1. Algorithm for proarrhythmia observations. CAPS = Cardiac Arrhythmia Pilot Study; NSVT = nonsustained ventricular tachycardia; PVC = premature ventricular complex; TdP = torsades de pointes; SVT = supraventricular tachycardia; VF = ventricular fibrillation.

patient/subjects, mainly comprised patients without arrhythmia. Most of these trials (142 of the 155) were conducted before 1980, enrolling mainly patients with hypertension (1,628), angina pectoris and a number of other clinical entities such as thyrotoxicosis and migraine.

Proarrhythmia: An algorithm was devised in which all patient case report forms were screened to ascertain possible instances of proarrhythmia (Fig. 1). All cases of sustained ventricular tachycardia, ventricular fibrillation or torsades de pointes (TdP), considered by the investigator to represent proarrhythmias, were so classified. All other episodes were then reviewed by Bristol-Myers' medical staff with particular attention to onset, severity, outcome and any additional mitigating or relevant data. If judged to have a probable relation, these cases were added to the group identified by the investigators. Cases in which the preponderance of evidence suggested recurrence of the arrhythmia being treated were excluded. For the less severe cases, e.g., increased total hourly number of ventricular premature complexes (VPCs) or increased number of episodes of nonsustained ventricular tachycardia, the same process was followed. If the investigator considered such occurrences to represent a proarrhythmia, they were so classified. If not, they were classified as proarrhythmia if they met the criteria developed for the Cardiac Arrhythmia Pilot Study (CAPS).[6] Cases not meeting these criteria were considered to represent random variability.

All cases classified as proarrhythmia were then divided between those that resulted in hemodynamic compromise or required urgent medical attention, or both, which were termed "severe," and those that had no or only mild symptoms, which were termed "nonsevere."

RESULTS

Current controlled arrhythmia trials—demographics: The study population was predominantly male (75%), Caucasian (88%) and middle-aged (mean 58.7 years). Thirty-five percent were age ≥65 years.

Type of arrhythmia: There was a substantial number of patients in each subcategory of arrhythmia, whether based on diagnosis or trial design (Table I). The largest

TABLE I Diagnosis and Design of Current Controlled Arrhythmia Trials

Disease and Trial Design	Studies	No. of Pts.
Complex ventricular arrhythmia		
Concurrent placebo control	2	182
Dose comparison	1	105
Historical control	1	47
Concurrent active drug	3	359
Total	7	693
Sustained VT		
Concurrent active drug	1	145
Historical control	1	236
Total	2	381
Supraventricular arrhythmia		
Concurrent placebo	1	42
Historical control	1	75
Concurrent active drug	1	97
Total	3	214
Total	12	1,288

VT = ventricular tachycardia.

TABLE II Medical History of Patients in Controlled Arrhythmia Trials

	No. of Pts. (%)* Total (n = 1,285)†
Hypertension	536 (42%)
Angina pectoris or coronary insufficiency, or both	479 (37%)
CAD with previous MI	548 (43%)
CAD without previous MI	135 (10%)
Valvular disease	225 (18%)
Idiopathic heart disease	100 (8%)
Cardiomegaly	321 (25%)
Congestive heart failure	235 (18%)
Second- or third-degree heart block	50 (4%)
Shock or circulatory collapse, or both	118 (9%)
Cardiomyopathy	146 (11%)
Cardioversion	383 (30%)

* For each cardiovascular history variable, the indication is based on the actual number of available data.
† Three patients had no available cardiovascular history.
CAD = coronary artery disease, MI = myocardial infarction.

single group consisted of patients with complex ventricular ectopy—693 patients, or 53.8% of the total. There were 381 patients (30%) with a diagnosis of sustained ventricular tachycardia and 214 treated with supraventricular arrhythmia, mainly atrial fibrillation.

Medical history: A substantial proportion of patients had significant cardiovascular history, including hypertension, angina, coronary artery disease and congestive heart failure (CHF) (Table II). As expected, patients with sustained ventricular tachycardia had the highest percentage of severe conditions, e.g., coronary artery disease (78%), CHF (38%), cardiomegaly (44%) and cardiomyopathy (20%); 77% underwent successful cardioversion (data not shown). Forty-nine percent of patients were in New York Heart Association (NYHA) functional class I, 44% in II, 8% in III and 1 patient was in class IV. Arrhythmias and heart disease had been present for many years in most patients (mean 3.5 years for arrhythmia and 6.5 years for heart disease).

Prior medicaton history: Medication prescribed before receiving sotalol was reflective of the high incidence of cardiovascular disease in the population. More than 60% of patients had received treatment with a wide variety of drugs, including class I antiarrhythmics (40%), β blockers (29%), cardiac glycosides (14%), calcium channel blockers (14%), coronary vasodilators (10%), as well as drugs for the treatment of hypertension (7%), nonthiazide diuretics (6%), thiazides (5%) and class III antiarrhythmics (3%).

Duration and dosage: Exposure to sotalol was prolonged enough to observe any late adverse events, with 389 patients treated 1 year or longer. The doses given ranged from 40 to 960 mg/day (in 2 divided doses), with most receiving 160 to 640 mg. Because this is the currently recommended dose range, the data obtained were a valid reflection of the response to doses that will be used in the general population.

Proarrhythmia: Among the 1,288 patients in the current controlled arrhythmia trials, 110 were identified by the algorithm (Fig. 1). Of these, 56 patients (4.3%) were considered to have possibly or probably drug-related proarrhythmic events (Fig. 2). The balance, 54 patients, had increased ectopy that met the CAPS criteria[6] for either increased VPC (43) or increased nonsustained ventricular tachycardia. (14) It was concluded that these cases reflected random variability and were not drug related because (1) all patients were without symptoms, (2) all continued to take sotalol, and (3) the incidence of increased ectopy was comparable to that found for placebo-treated patients in the CAPS trial.[6]

Of the 56 patients with drug-related putative proarrhythmic events, 27 had severe episodes: sustained ventricular tachycardia (9), ventricular fibrillation (6) and TdP with hemodynamic compromise (12). Their outcome was discontinuation (20), death (3) or continuation at the same dose after insertion of pacemaker or at a decreased dose (4).

Other investigator-noted proarrhythmias of a nonsevere nature occurred in 29 patients. The dubious relation to sotalol and the mild nature of the putative proarrhythmic event was underscored by the fact that 38% continued to take sotalol (Fig. 2).

Torsades de pointes: Among the 56 patients with proarrhythmia in whom proarrhythmia developed, 24 had TdP, an overall incidence of 1.9%. As noted previously, TdP was associated with hemodynamic compromise in one-half of the patients, but there were no fatalities. Eighteen of the 24 patients had a history of sustained ventricular tachycardia, and the same number had a history of myocardial infarction or cardiomyopathy, or both.

No systematic relation could be found with hypokalemia, long QT, bradycardia or other commonly associated factors. However, in individual cases, 1 or more of these factors was clearly associated. More frequently, borderline abnormal values of 2 or 3 of the provocative factors appeared to be related.

Relation to QT interval: The association between baseline and on-therapy QT and QTc values was examined by comparing the values of patients with severe proarrhythmias with those of the balance of the study patients (Fig. 3). Of the patients destined to experience a severe proarrhythmia, the mean baseline QT and QTc were 33.7 and 26.9 ms longer, respectively, than those values for the comparison group (Fig. 3). The QTc difference was highly statistically significant ($p = 0.0029$), but that for QT was not ($p = 0.08$) because of the wider variability. The QTc difference was not due to different heart rate (72.9 ± 0.4 vs 71.5 ± 3.4 beats/min, $p = 0.67$). Similarly, in a small number of patients (16) who had an electrocardiogram recorded within 1 week of the proarrhythmic event, the QT and QTc were 28.2 and 22.4 ms longer, respectively, when compared with the mean maximal on-therapy values for patients not experiencing a severe proarrhythmia. These differences did not quite reach statistical significance ($p = 0.057$ and 0.078, respectively) due to the wide variability (large standard error of the mean), but some patients had clearly prolonged intervals.

Congestive heart failure: Nineteen patients (1%) discontinued therapy with sotalol in the controlled arrhyth-

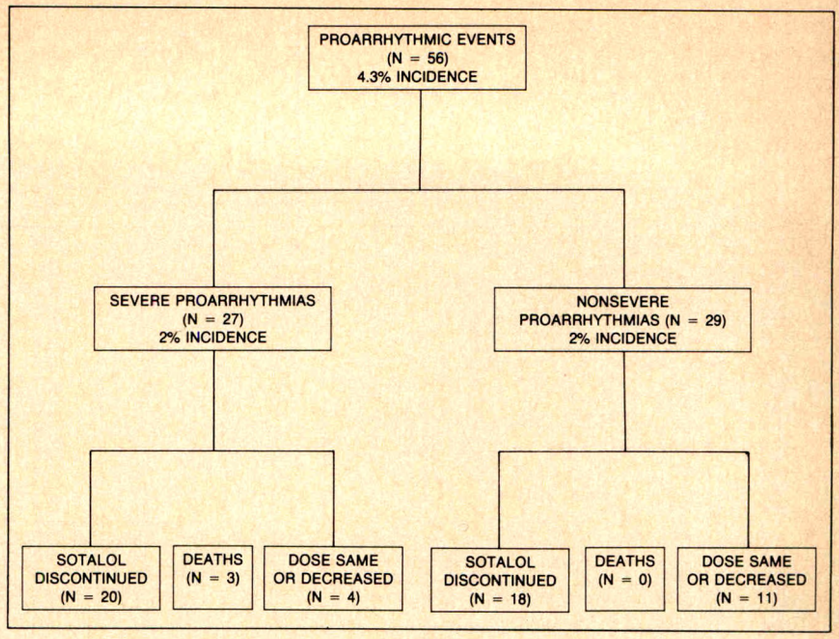


FIGURE 2. Drug-related proarrhythmia in current controlled arrhythmia trials.

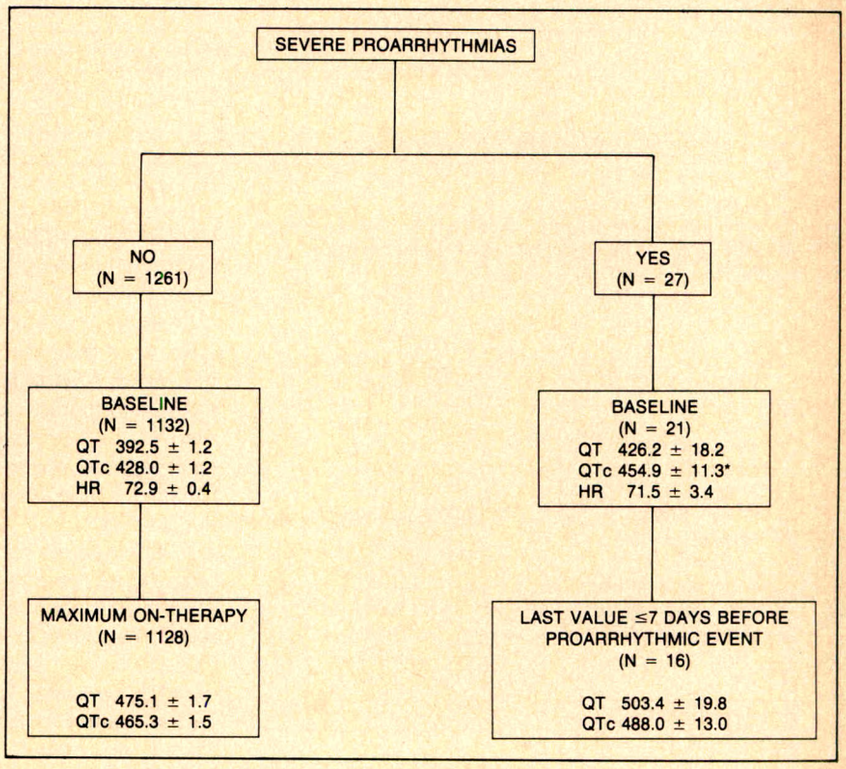


FIGURE 3. Comparison of mean baseline and on-therapy QT and QTc—patients with severe proarrhythmia compared with patients without proarrhythmia. Values are mean ± standard error of the mean; QT and QTc are measured in milliseconds and heart rate (HR) in beats/minutes. *QTc at baseline differs significantly between groups, p = 0.0029. All other comparisons were not statistically significant.

mia trials due to drug-related CHF (Table III). All were men, and 53% were age ≥65 years. Only 4 of the 12 patients who underwent a baseline ejection fraction determination had an ejection fraction in the normal range (45%). Other contributory conditions included a history of CHF (10), cardiomyopathy (6) and cardiomegaly (10). CHF developed in 7 patients within 7 days and in an additional 11 patients within 30 days of initiating sotalol. Their median total daily dose was 320 mg.

Premature drug discontinuation: The most common reasons for premature discontinuation of a drug were: ineffective treatment (22%), adverse effects (16%) and administrative reasons (8%), followed in frequency by a variety of miscellaneous causes (Table IV). The incidence of discontinuation for lack of efficacy was highest among patients treated for sustained ventricular tachycardia (39%) vs only 8% among those treated for complex ectopy. The opposite relation was true for discontinuation

TABLE III Patients Discontinuing Therapy Because of Drug-Related Congestive Heart Failure in Current Controlled Arrhythmia Trials

Age (yr) Sex	Baseline EF/NYHA Class	History of CHF	History of Cardiomyopathy	Cardiomegaly at Baseline	Total Daily Dose at Onset (mg)	Dose Duration at Onset (days)	Therapy Duration at Onset (days)
Patients with Ventricular Arrhythmia (n = 693)							
68M	—/II	Y	Y	Y	320	6	6
63M	—/II	Y	N	Y	320	4	4
68M	—/I	N	N	N	160	<1	<1
63M	61/I	N	N	N	320	2	29
51M	47/II	N	N	Y	320	7	7
63M	—/II	Y	Y	Y	320	4	4
73M	52/I	N	N	Y	320	10	10
65M	43/II	Y	N	N	320	16	16
61M	39/II	Y	Y	N	320	8	8
50M	21/II	Y	N	N	320	6	6
70M	—/I	N	N	Y	320	10	10
59M	30/II	N	N	N	480	5	11
Patients with Sustained Ventricular Tachycardia (n = 381)							
65M	44/II	Y	N	Y	640	21	21
60M	35/II	Y	Y	Y	320	1	1
58M	54/II	Y	Y	N	80	1	80
74M	40/I	N	N	Y	320	15	17
75M	34/III	Y	Y	Y	160	8	8
Patients with Supraventricular Arrhythmia (n = 214)							
69M		NA	N	NA	160	NA	9
66M		NA	N	NA	320	NA	9

EF = ejection fraction; NA = not available; NYHA = New York Heart Association classification.

TABLE IV Reasons for Premature Discontinuation from Current Controlled Arrhythmia Trials

Reason	Total No. (%) of Patients Discontinued (n = 1,293)*
Ineffective	280 (21.7%)
Adverse effect	211 (16.3%)
Administrative	103 (8.0%)
Patient moved	31 (2.4%)
Proarrhythmia	31 (2.4%)
Patient died	30 (2.3%)
Intercurrent illness	11 (0.9%)
Arrhythmia resolved	6 (0.5%)
Worsening of disease	1 (0.1%)
Alternative therapy	2 (0.2%)
Other	13 (1.0%)
Total	719 (55.6%)

* Five patients reentered trials.

due to adverse effects: 11% among patients with sustained ventricular tachycardia vs 21% among patients with ventricular ectopy. Presumably, in patients with life-threatening arrhythmias, both patient and physician were willing to tolerate mild and moderate adverse effects. Most patients who had discontinued treatment for administrative reasons had completed the double-blind portion but, for a variety of reasons, elected not to enter the long-term extension of the trial. Proarrhythmia caused discontinuation in 2.4% of patients, a figure consistent with the identification and classification of "severe" cases by the algorithm previously discussed.

Further examination of the most frequent adverse effects and those associated with premature discontinuation is presented in Table V. In the cardiovascular system, dyspnea and bradycardia were the most common and, in most cases, were considered drug-related effects by the investigators. These various cardiovascular adverse effects resulted in discontinuation of 1 to 4% of the population at risk.

Among the noncardiac adverse effects, fatigue, dizziness and asthenia were the most common, and each resulted in discontinuation of 1.9 to 3.6% of the patients at risk. Gastrointestinal effects, namely, nausea/vomiting and diarrhea, occurred infrequently, each causing discontinuation in about 1% of patients.

Laboratory examinations: Serial batteries of serum chemistries, hematology and urinalysis were obtained. From this enormous data base, key variables were selected for presentation (Table VI). Examination of the median percent change from baseline of both the maximal test value and the last test value recorded while the patient was taking the drug failed to reveal any generalized trend, with the possible exception of triglycerides, which tended to increase. Considering that these values include nonfasting determinations, the increase is probably insignificant ($p < 0.001$). However, the increase was modest, from 182 ± 9.2 mg/dl at baseline to 202 ± 68 mg/dl at

TABLE V Most Frequent Adverse Effects of Sotalol in the Current Controlled Arrhythmia Trials

	No. of Pts. Discontinuing	No. of Pts. Reporting While on Sotalol	Percent of Pts. Discontinuing Who Reported	Percent of Pts. Discontinuing Because of any Adverse Effects (n = 211)	Percent of Pts. Discontinuing from the Population at Risk (n = 1,288)
Cardiovascular					
Dyspnea	50	247	20.2	23.7	3.9
Bradycardia	31	111	27.9	14.7	2.4
Chest pain	20	217	9.2	9.5	1.6
Heart failure	16	27	59.3	7.6	1.2
Palpitations	13	204	6.4	6.2	1.0
Nervous					
Fatigue	46	273	16.8	21.8	3.6
Dizziness	30	273	11.0	14.2	2.3
Asthenia	24	148	16.2	11.4	1.9
Headache	8	127	6.3	3.8	0.6
Gastrointestinal					
Nausea/vomiting	17	124	13.7	8.1	1.3
Diarrhea	10	86	11.6	4.7	0.8

TABLE VI Summary Statistics For Selected Laboratory Test Results in the Current Controlled Arrhythmia Trials

		Median Percent Change from Baseline		Incidence of Above-Normal On-Sotalol Test Values*	
Laboratory Test Variable	No.	Maximal Test Value (%)	Last Test Value (%)	Max. Test Value On-Sotalol Baseline (%)	Last Test Value On-Sotalol Baseline (%)
Alkaline phosphatase	599	3.7	−3.8	42/501 (8.4)	30/499 (6.0)
Total bilirubin	629	25.0	12.5	35/578 (6.1)	24/574 (4.2)
SGOT	718	10.7	0.0	65/617 (10.5)	38/612 (6.2)
SGPT	510	8.7	0.0	40/393 (10.2)	20/390 (5.1)
Triglycerides	341	31.1	17.8	68/190 (35.8)	49/192 (25.5)
Cholesterol	444	6.8	2.8	50/370 (13.5)	31/369 (8.4)
Creatinine	724	0.0	0.0	52/619 (8.4)	30/616 (4.9)
BUN	92	8.0	0.8	6/75 (8.0)	5/75 (6.7)

* Incidence = number of patients with on-sotalol test values above normal limits divided by the number of patients whose baseline values were within or below normal limits. Investigator's normal laboratory ranges were used.
BUN = blood urea nitrogen; Max. = maximal; SGOT = serum glutamic oxaloacetic acid; SGPT = serum glutamic pyruvic transaminase.

the last test. Similarly, serum cholesterol increased only slightly, from 212 ± 2.1 to 219 ± 2.1 mg/dl ($p < 0.001$). The incidence of above-normal on-sotalol test values, examining either the maximum ever recorded or the most recent value, again revealed no general trend, with the possible exception of triglycerides.

Five patients discontinued therapy because of abnormal laboratory values. In 4, no relation could be ascertained between the abnormal laboratory values and sotalol administration. In the fifth, a highly plausible explanation for a modest increase in the white blood cell count was present.

Other patient groups: In the remaining arrhythmia studies (miscellaneous, supportive and retrospective), there were 9 cases of severe proarrhythmia, an incidence of 1.2% (Table VII); in the early, mainly nonarrhythmic clinical studies group, the incidence was 0.08% (3 of 3,831). Thus, the overall incidence of severe proarrhythmia in the clinical trials was 0.7% (39 of 5,856).

Among the 39 cases of severe proarrhythmia, 19 (49%) were of the TdP form. Thus, the overall incidence of TdP was 0.3%. In all cases of TdP (severe and nonsevere), the incidence was 0.5%.

TABLE VII Occurrence of Proarrhythmia and Discontinuation Because of Adverse Effects in Sotalol Clinical Trials

Clinical Trials Group	No. of Pts. Enrolled	Severe Proarrhythmia No. (%)	Discontinuation Because of Adverse Effect No. (%)
Current controlled arrhythmia	1,288	27 (2.1)	211 (16)
Miscellaneous controlled arrhythmia	136	1 (0.7)	24 (18)
Supportive arrhythmia	147	4 (2.7)	21 (14)
Retrospective arrhythmia	454	4 (0.9)	27 (6)
Nonarrhythmia	3,831	3 (0.08)	286 (7)
Total	5,856	39 (0.7)	569 (10)

Adverse effects caused discontinuation of 6 to 18% of patients in the various clinical trial groups, with an overall incidence of 10% (Table VII).

DISCUSSION

The evaluation of safety of any therapeutic agent is obtained by a careful assessment of the benefit:risk ratio, given that all drugs have adverse effects. The benefit side of the equation consists of the direct benefits of drug therapy to the patient as well as the relative benefits of the particular drug in question, compared with other drugs used for treatment of the same of similar condition.

Benefits of therapy: The benefits of the treatment of arrhythmias are several. First, appropriately directed antiarrhythmic therapy can prolong life in patients with malignant ventricular arrhythmias,[7–9] although this is often difficult to demonstrate in any antiarrhythmic agent. Sotalol prevents induction of ventricular tachycardia by programmed electrical stimulation and reduces recurrences[10–13] and thus likely enhances survival. Prevention of ventricular fibrillation has been demonstrated in a conscious canine model of sudden cardiac death.[14] Second, sotalol decreases the occurrence of nonfatal arrhythmias causing symptoms associated with hemodynamic compromise, such as syncope and lightheadedness (Bristol-Myers Company, unpublished observations).

Third, sotalol decreases symptoms that are annoying and sometimes disabling, such as palpitations and dizziness. Here, the indication for treatment rests on less objective grounds, yet symptom relief is a fundamental therapeutic goal.

Risks of therapy: The data presented indicate that the risk and adverse effects complicating sotalol therapy stem from its properties as a β blocker and its propensity to prolong cardiac repolarization.

Proarrhythmia: The proarrhythmic risk of sotalol is less than that of many currently marketed antiarrhythmic agents.[15,16] This is true despite the occurrence of TdP,[17–20] which is noteworthy chiefly because it is the form of proarrhythmia most easily recognizable as drug related.[21] The rather low incidence (1.9%) in the current controlled arrhythmia trials, with one-half of the cases being self-limiting and causing few symptoms, indicates that this reaction is not a major safety issue. Among those patients who did have severe (hemodynamically compromising) TdP, the episodes were either self-terminating or controlled by the widely available and routine measures of temporary pacing, intravenous magnesium sulfate, adjusting the rate of a permanent pacemaker, infusion of isoproterenol or a combination of these. In only 6 cases was direct-current cardioversion used. Consistent with reports of TdP with quinidine[22] or drug-associated ventricular fibrillation,[23] TdP occurred soon after initiation of sotalol or after an increase in dose. Most episodes occurred in patients with major cardiac disorders plus a history of sustained ventricular tachycardia/ventricular fibrillation. Because standard practice dictates that therapy be initiated in the hospital for such patients, TdP would be detected by telemetry or Holter monitoring, and prompt management instituted. In addition, the risk of initiating TdP probably can be minimized by avoidance of hypokalemia, excessive QT prolongation and bradycardia. Maintaining serum potassium concentrations at $\geq$4.0 mmol/liter as a means of reducing proarrhythmia with all antiarrhythmic agents has been suggested.[23]

Congestive heart failure: The long-standing concern in the medical community about administration of β blockers to patients with heart failure prompted detailed examination of the tolerance of patients with left ventricular dysfunction to sotalol. In the controlled arrhythmia trials, there were 235 patients with a medical history of CHF (44% in NYHA class II, 8% in NYHA class III). Overall, the discontinuation of sotalol therapy for new or worsened CHF was only 1.5%. Although cautious dose titration, judicious use of nonthiazide diuretics and serial examinations are indicated to avoid precipitation of CHF, the risk does appear to be as great as had been anticipated based on current dogma.

Beta blockade: Sotalol has adverse effects that relate to its β-blocking activity. Bradycardia led to discontinuation of therapy in 35 patients (2.7%). A wide range of physicians have extensive experience with β blockers; their familiarity with the management of β-blockade effects (e.g., by dose reduction, pacemaker implantation and reduction of concomitant medication) gives considerable confidence that these adverse effects will not prove unduly burdensome to the physician or present excessive risk to the patient. Beta blockade produced by sotalol provides numerous benefits to the patient with cardiac disease, being anti-ischemic, reducing blood pressure and reducing the rate of reinfarction and mortality after myocardial infarction.[24]

CONCLUSIONS

Sotalol possesses a well-characterized safety profile, with the principal adverse effects being (1) dyspnea, bradycardia and fatigue, i.e., responses inherent in β blockers because they are extensions of the pharmacology; (2) proarrhythmia, most clearly defined when manifest as TdP; and (3) worsening of CHF in about 2%. The risk of severe proarrhythmia was relatively modest (2%) and occurred chiefly among patients treated for sustained ventricular tachycardia. Therapy in these patients is initiated under close medical supervision, and any such episodes are managed by standard hospital procedures. Although TdP had an overall incidence of 0.3% in all patients (1.9% in the current arrhythmia clinical trials), only one-half of these occurrences were associated with hemodynamic compromise. TdP with sotalol has not resulted in a fatal outcome in the clinical trials or among any of the approximately 30 patients reported on. Moreover, the favorable risk:benefit ratio of sotalol is striking compared with amiodarone, the only other available oral class III antiarrhythmic drug.

Acknowledgment: We acknowledge the cooperation of the several hundred physicians, nurses and study personnel who contributed to development of sotalol during the past 2 decades. Their carefully completed case report forms were the source of this safety analysis. Assessment of the safety data base was achieved by the joint efforts of

the Clinical Cardiovascular and Biostatistics/Data Management departments especially Don Archibald, Barbara Conetta, Judd Andres and Linda Kudrick. We also thank Agnes Murch and Ann Collins for their secretarial assistance in the preparation of this manuscript.

REFERENCES

1. Lish PM, Weikel JH, Dungan KW. Pharmacological and toxicological properties of two new beta-adrenergic receptor antagonists. *J Pharmacol Exp Ther 1985;149:161–173.*

2. Kaumann AJ, Olson CB. Temporal relation between long lasting after contractions and action potentials in cat papillary muscle. *Science 1968;161:293–295.*

3. Singh BN, Vaughn Williams EM. A third class of anti-arrhythmic action: effects on atrial and ventricular intracellular potentials, and other pharmacological actions on cardiac muscle, of MJ1999 and AH3474. *Br J Pharmacol 1970;39: 675–689.*

4. Singh BN, Nademanee K. Sotalol: a beta-blocker with unique antiarrhythmic properties. *Am Heart J 1987;114:121–139.*

5. Singh DN, Deedwania P, Nademaneee K, Ward A, Sorkin EM. Sotalol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use. *Drugs 1987;34:311–349.*

6. The Cardiac Arrhythmia Pilot Study (CAPS) investigators. Effects of encainide, flecainide, imipramine and moricizine on ventricular arrhythmias during the year after acute myocardial infarction: the CAPS. *Am J Cardiol 1988;61:501–509.*

7. Graboys TB, Lown B, Podrid PJ, DeSilva R. Long-term survival of patients with malignant ventricular arrhythmia treated with antiarrhythmic drugs. *Am J Cardiol 1982;50:437–443.*

8. Swerdlow CD, Winkle RA, Mason JW. Determinants of survival in patients with ventricular tachyarrhythmias. *N Engl J Med 1983;308:1436–1442.*

9. Waller TJ, Kay HR, Speilman SR, Kutalek SP, Greenspan AM, Horowitz LN. Reduction in sudden death and total mortality by antiarrhythmic therapy evaluated by electrophysiologic drug testing: criteria of efficacy in patients with sustained ventricular tachyarrhythmia. *JACC 1987;10:83–89.*

10. Senges J, Lengfelder W, Jauernig R, Czygan E, Brachmann J, Rizos I, Cobbe S, Kubler W. Electrophysiologic testing in assessment of therapy with sotalol for sustained ventricular tachycardia. *Circulation 1984;69:577–583.*

11. Nademanee K, Feld G, Hendrickson J, Singh PN, Singh BN. Electrophysiologic and antiarrhythmic effects of sotalol in patients with life-threatening ventricular tachyarrhythmias. *Circulation 1985;72:555–564.*

12. Steinbeck G, Bach P, Haberl R. Electrophysiologic and antiarrhythmic efficacy of oral sotalol for sustained ventricular tachyarrhythmias: evaluation by programmed stimulation and ambulatory electrocardiogram. *JACC 1986;8:949–958.*

13. Singh SN, Cohen A, Chen Y, Wish M, Thoben-O'Grady L, Peralba J, Gottdiener J, Fletcher RD. Sotalol for refractory sustained ventricular tachycardia and nonfatal cardiac arrest. *Am J Cardiol 1988;62:399–402.*

14. Lynch JJ, Coskey LA, Montgomery DG, Lucchesi BR. Prevention of ventricular fibrillation by dextrorotatory sotalol in a conscious canine model of sudden coronary death. *Am Heart J 1985;109:949–958.*

15. Velebit V, Podrid PJ, Lown B, Cohen BH, Graboys TB. Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs. *1982;65:886–894.*

16. Poser RF, Podrid PJ, Lombardi F, Lown B. Aggravation of arrhythmia induced with antiarrhythmic drugs during electrophysiologic testing. *Am Heart J 1985;110:9–16.*

17. McKibbin JK, Pocock WA, Barlow JB, Scott Millar RN, Obel IWP. Sotalol, hypokalemia, syncope and torsade de pointes. *Br Heart J 1984;51:157–162.*

18. Krapf R, Gertsch M. Torsade de pointes induced by sotalol despite therapeutic plasma sotalol concentrations. *Br Med J 1985;290:1784–1785.*

19. Kuck KH, Kunze KP, Roewer N, Bleifeld W. Sotalol-induced torsade de pointes. *Am Heart J 1984;107:179–180.*

20. Mattioni T, Zheutlin T, Sarmiento J, Parker M, Dunnington C, Reilly K, Larsen K, Nebergall N, Kehoe R. Sotalol mediated torsade de pointes (abstr). *JACC 1988;11:168A.*

21. Dessertenne F, Coumel P, Fabiato A. Fibrillation ventriculaire et torsades de pointes. *Presse Med 1969;77:193–196.*

22. Bhandari A, Siddiqi R, Jamison M, Rahimtoola SH. Antiarrhythmic drug-induced torsade de pointes: lack of relationship to marked QT prolongation (abstr). *JACC 1988;11:56A.*

23. Minardo JD, Heger JJ, Miles WM, Zipes DP, Prystowsky EN. Clinical characteristics of patients with ventricular fibrillation during antiarrhythmic drug therapy. *N Engl J Med 1988;319:257–262.*

24. Yusef S, Peto R, Lewis J, Collins R, Sleight P. Beta-blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis 1985;27:335–371.*

Discussion IV: Supraventricular Arrhythmias

Dr. Bramah Singh (Los Angeles, California): Dr. Camm has provided a succinct review of the emerging role of sotalol in supraventricular tachyarrhythmias. Dr. Camm, do you think that the mechanism of prevention or reduced incidence of recurrence of atrial fibrillation induced by sotalol is related to the class III action of sotalol on the atrial tissue, or are there other mechanisms involved?

Dr. A. John Camm (London, United Kingdom): That is obviously a question that cannot be answered from a simple review of the data on the efficacy of the compound. Undoubtedly, any drug that will make the atrial myocardium more homogeneous in terms of its recovery should reduce the probability of atrial fibrillation. Certainly, in the Wolff-Parkinson-White setting, or where there is a concealed bypass tract present, one would anticipate that blocking conduction would prevent early echoes and would prevent the arrhythmias; the extension of the refractory period, of course, is not sufficient. We need to know what effect it has on the relative refractory period and the vulnerable period within that context. Do you have any other ideas?

Dr. Singh: No, I was just asking if there were any studies to support the mechanisms that you mentioned. Do you know of any studies that have looked at their validity?

Dr. Camm: I am not aware of any studies in that area. I know of many studies, but not with sotalol.

Question: Dr. Camm, I found your data on atrial fibrillation fascinating. It is such a large area of arrhythmia management, perhaps with the highest morbidity for the largest number of people; I was very impressed by your figures with paroxysmal atrial fibrillation and sotalol. Do you think sotalol offers us something new in comparison to class I drugs?

Dr. Camm: Many of the patients included in this multicenter study had class I agents, and I presume that they were not effectively controlled with those agents. As such, therefore, sotalol seems to offer an additional dimension. However, when the comparison was made between quinidine and sotalol in the postcardioversion setting, there was no clear difference between the 2 drugs. I do not think that one necessarily needs a numerical difference, as long as there is a different spectrum of action, and a different group in which the drug will be efficacious. In my clinical experience, sotalol is a very effective agent for the management of paroxysmal atrial fibrillation. It is one that I use as a first choice and to be free of the potential problems that can occur with flecainide; I think the class IC drugs are the next best compounds for the management of paroxysmal atrial fibrillation. Therefore, I choose sotalol first and then something like flecainide, encainide or propafenone.

Dr. Singh: Dr. Camm, I have always been interested in the relative importance of changes in conduction vs refractoriness as a component of the mechanism mediating the salutary effects in the control of cardiac arrhythmias in general. In this context, I have always thought that lengthening of the action potential duration is the way to convert atrial fibrillation to sinus rhythm. We see more and more data, albeit relatively uncontrolled, on the effectiveness of the class IC drugs in this context. If I were to ask you to take a typical β blocker, sotalol, and a class IC drug such as flecainide or encainide, and do a randomized study in people with chronic atrial fibrillation, how do you think the efficacy results might turn out? I am not alluding to the issue of maintaining stability of sinus rhythm, but merely to acute conversion. We studied procainamide many years ago at Cedars-Sinai Medical Center.[1] A significant percentage of patients were converted by procainamide, which happens to have class I and class III actions. Would you care to speculate?

Dr. Camm: I think that it would be a close race between flecainide, which has a predominant effect on conduction, and sotalol, which has a predominant effect on repolarization. Both of them would be far superior to digoxin or β blockade. However, I do not know whether sotalol or a class IC compound would be the most effective at converting established atrial fibrillation.

Dr. Elliott Entman (Boston, Massachusetts): I would like to comment that we have had experience with persons who are refractory to conventional therapy like a class I agent. We were quite impressed with the efficacy of sotalol, not only in those who had failed on the conventional class IA agent, but also in those who had failed on propafenone. Also, essentially in those persons who had failed on propafenone, we then gave them sotalol for the treatment of both paroxysmal and chronic atrial fibrillation; 50% of these patients were controlled with sotalol, leading us to believe that it might be interesting to give sotalol as the first agent in this kind of trial.

Dr. Camm: I am not certain what would happen if you did it the other way. You may well have had the same sort of results.

Dr. Entman: That is right; we need to randomize the first drug. In terms of percent conversion of chronic atrial fibrillation, we observed about a 25% incidence of pharmacologic conversion with sotalol, but I would like to point out that we pushed the doses a little higher than what was reported in the Swedish multicenter study comparing quinidine and sotalol. With careful monitoring of the QTc interval, we increased the dosage to 480 mg

twice a day as long as there were no β-blocker-related side effects and where the QTc did not exceed 500 ms. I also think that perhaps increasing the drugs a little higher allowed us to achieve that rate of conversion.

Dr. Singh: Dr. Camm, I am not sure I understood your comment as to the effect of class IC agents on conversion of atrial fibrillation. Why would a drug that prolongs conduction convert atrial fibrillation?

Dr. Camm: That was not my point. My point was that it does convert atrial fibrillation and it does predominantly affect conduction within the atrium, compared with its effect on the refractory period of the atrium.

REFERENCES

1. Halpern SW, Ellrodt G, Singh BN, Mandel WJ. Efficacy of intravenous procainamide infusion in converting atrial fibrillation to sinus rhythm: relation to left atrial size. *Br Heart J 1980;44:589–595.*

Expanding Clinical Role of Unique Class III Antiarrhythmic Effects of Sotalol

Bramah N. Singh, MD, DPhil

The concept of controlling cardiac arrhythmias by prolonging repolarization was first exemplified in the electrophysiologic properties of sotalol. It has since been shown to be a property shared by an increasing number of compounds. Sotalol has an additional propensity for blocking β receptors; therefore, its net effects in controlling arrhythmias result from its β-blocking actions as well as lengthening the refractory period of cardiac muscle. The properties of amiodarone, another class III agent, are even more complex. The potency of these 2 agents must therefore be distinguished from the so-called "pure" class III agents, which may exhibit a more restricted spectrum of action. Available data indicate that prolonged QT interval (the correlate of prolonged cardiac repolarization) merely provides the substrate for antifibrillatory and proarrhythmic actions relative to the absence or presence of associated pharmacologic properties of the compounds or to the clinical setting in which these compounds are used. Thus, class III agents might be expected to exhibit a variable spectrum of efficacy as antifibrillatory drugs with an equally variable incidence of torsades de pointes and so induce a proarrhythmic effect. An understanding of the mechanisms underlying these differences, especially at a cellular level, may provide the basis for the development of newer, clinically relevant antiarrhythmic and antifibrillatory compounds.

(Am J Cardiol 1990;65:84A–88A)

From the Division of Cardiology, Wadsworth Veterans Administration Hospital and the Department of Medicine, University of California at Los Angeles School of Medicine, Los Angeles, California. This work was supported in part by grants from the American Heart Association, the Greater Los Angeles Affiliate, and Medical Research Funds of the Veterans Administration, Washington, D.C.

Address for reprints: Bramah N. Singh, MD, Section of Cardiology, 691/111E, Wadsworth Veterans Administration Hospital, Wilshire and Sawtell Boulevards, Los Angeles, California 90073.

The data presented in the symposium proceedings clearly indicate that diverse supraventricular and ventricular arrhythmias can be controlled effectively by using sotalol. It is widely appreciated that sotalol is a potent β blocker. However, now it is also clear that the drug is not just another β blocker; it belongs to the class of agents that markedly lengthen cardiac repolarization, with a corresponding increase in the effective refractory period and little or no effect on conduction. Indeed, it is the prototype of class III antiarrhythmic agents.[1] The data show that the overall antiarrhythmic effects of sotalol may be separable, although not readily, in terms of the effects that stem from its β-blocking actions and those that arise from its propensity to prolong the cardiac action potential. The purpose of this final report in the proceedings is to examine critically the issues that appear important in terms of the electrophysiologic determinants of antiarrhythmic efficacy and the proarrhythmic effects of drugs that appear to act selectively by primarily prolonging myocardial repolarization.

There is a growing plethora of agents that lengthen cardiac repolarization; until very recently, there were few "pure" substances that prolonged repolarization and refractoriness without inducing a change in other electrophysiologic properties. The known agents exhibit a variable spectrum of not only antiarrhythmic efficacy but also an equally variable propensity to induce torsades de pointes—the most specific and striking proarrhythmic effect associated with prolonged repolarization. The question has therefore arisen as to the circumstances in which prolonged QT interval on the surface electrocardiogram constitutes an antiarrhythmic mechanism and when it is proarrhythmic.[2]

ANTIARRHYTHMIC EFFICACY AND PROLONGED REPOLARIZATION

The efficacy of sotalol should be judged in light of its property as a β blocker and as a compound that markedly prolongs voltage-dependent refractoriness. Table I presents a qualitative summary of the antiarrhythmic actions of sotalol compared with those of conventional β blockers. It is evident that the spectrum of arrhythmias responding to the drug acutely and after chronic therapy is wider than that for conventional β antagonists and is predictable from its electrophysiologic properties.[3,4]

Supraventricular arrhythmias: Certain issues merit emphasis with respect to the role of sotalol in the control of supraventricular tachyarrhythmias. For example, it appears that in the acute conversion of atrial fibrillation and flutter, the so-called class III actions of sotalol are likely to be critical. However, further controlled trials

should be performed to confirm that the drug is more effective than conventional β blockers. The use of d-sotalol in this setting is likely to delineate the significance of adrenergic blockade, if any, in the acute conversion of atrial flutter fibrillation. Sotalol is also effective in exerting not only an antifibrillatory effect in the case of atrial fibrillation complicating preexcitation syndromes, but also in slowing the frequency of the fibrillatory impulses reaching the ventricle as a result of an increased refractory period. The possibility of a depressant effect on anterograde conduction in this setting cannot be excluded, since at high concentrations the drug is known to inhibit the fast sodium channel.[5] In this context conventional β blockers are without effect. Because sotalol prolongs the refractory period in atria, it is likely to be effective in maintaining sinus rhythm in patients with atrial flutter and fibrillation converted to sinus rhythm either chemically or electrically. However, definitive data in this area are few.

Again, controlled, blinded clinical trials need to be performed to determine the precise efficacy of sotalol compared with class IA agents (such as quinidine, procainamide and disopyramide), which appear to work by altering conduction as well as refractoriness. Such trials, involving a comparison between sotalol and class IC agents such as flecainide and encainide (working essentially by slowing conduction), will also be of much theoretical and practical importance.

Experimental data indicate the presence of multiple reentrant loops within the atrium that provide the basis for atrial fibrillation.[6] The prospect for the acute conversion to sinus rhythm is low when there are numerous reentrant circuits. If one considers the leading circle hypothesis as the basis of the arrhythmia, the number of reentrant circuits will depend on the size of the atrium; it will also be inversely proportional to the refractory period of the atrium. Thus, agents that prolong the atrial refractory period and slow conduction velocity are likely to be most effective in terminating atrial flutter and fibrillation.[6]

It is well established that β blockers slow the ventricular response in atrial flutter and fibrillation by blocking adrenergic impulse traffic at the atrioventricular (AV) node; it is not clear whether such an effect is likely to be augmented by the additional class III effect of sotalol. However, purely on the basis of electrophysiologic considerations, this appears unlikely. The availability of the so-called pure class III agents devoid of autonomic effects (e.g., UK 66,798, E-4031 and sematilide) will be helpful in resolving this issue. Similarly, it is uncertain whether sotalol has a more potent effect in the acute termination of reentrant supraventricular tachycardias involving the AV node in the anterograde limb of the reentrant circuit, or whether the drug might be more effective than a conventional β blocker in reducing the recurrences of these arrhythmias during chronic prophylactic therapy. Here again, the issue is the role of changes in conduction vs those in refractoriness as the principal determinants of salutary effects in preventing reentrant supraventricular arrhythmias. In experimental models[7] and in humans,[8] d-sotalol, essentially a pure class III agent devoid of β-blocking activity, had little effect on AV nodal conduction or refractoriness.

TABLE I Comparative Antiarrhythmic Spectrum of Action of Sotalol and Conventional Beta Blockers Relative to Induction of Torsades

Type of Arrhythmia	Sotalol	Conventional β Blocker (Reference: Propranolol)
Supraventricular		
PSVT (reentrant): acute termination after i.v. injection	++	++
PSVT oral prophylaxis	++	++
Atrial flutter/fibrillation Acute conversion		
Sinus rhythm after i.v. injection	+++	±
Atrial flutter/fibrillation chronic prophylaxis of stability of sinus rhythm	++	±
Slowing of ventricular response (acutely and chronically) in atrial fibrillation	+++	+++
Atrial flutter/fibrillation complicating WPW syndrome (slowing of ventricular response and preventing recurrence of the arrhythmia)	++	0 (potential for aggravation)
Ventricular		
VPC suppression	++ (?+++)	++
VT/VF (spontaneous)	++	±
VT/VF (inducible by PES)	++ (?+++)	±
Reduction in sudden death in after-MI	++	++
Induction of torsades de pointes (%)	5	0

i.v. = intravenous; MI = myocardial infarction; PES = programmed electrical stimulation; PSVT = paroxysmal supraventricular tachycardia; VPC = ventricular premature complexes; VT/VF = ventricular tachycardia/fibrillation.
The range 0 to +++ indicates no effect to maximal effect possible after drug therapy. The net effects of sotalol represent a summed result of its β-blocking and antifibrillatory actions. The conclusions summarized here represent impressions based on uncontrolled and often limited data but are in line with the electrophysiologic actions of the drugs.

Class III action and suppression of ventricular arrhythmias: The critical issue is to what extent the so-called pure class III antiarrhythmic action contributes to the observed beneficial effect of the known class III agents in the suppression of (1) ventricular premature complexes (VPCs), and (2) either spontaneously occurring ventricular tachycardia/fibrillation or the arrhythmias inducible by programmed electrical stimulation of the heart. The effects of sotalol in these 2 categories of ventricular arrhythmias have been discussed in the proceedings. What has not clearly emerged from the studies reported here is the link between class III effects and the observed antiarrhythmic effects of sotalol.

It is interesting that in a double-blind, comparative study involving propranolol and sotalol, the VPC suppressant effect of sotalol was significantly (although slightly) greater than that of propranolol.[9] In other reports the difference is not as clearly evident. Therefore, the question is not settled as to whether the apparently greater effect of sotalol is due to its class III actions. This appears

to be inherently unlikely from electrophysiologic considerations.

Evidence indicates that "isolated" prolongation of the action potential duration has little or no effect on VPCs. For example, for the serotonin antagonist ketanserin, which lengthens repolarization,[10] Zehender et al[11] found that suppression of VPCs with placebo and ketanserin were indistinguishable statistically. Thus, it appears that the so-called class III action, per se, might be devoid of significant antiectopic propensity. The 2 class III agents, sotalol and amiodarone, the properties of which were greatly exploited by Singh and Vaughan Williams[1,12–14] to promulgate the concept of class III antiarrhythmic action, are pharmacologically complex and their antiectopic activity might stem from other electrophysiologic properties. However, one may reasonably argue that they have a greater potency for suppression of VPCs[2] because they induce a much greater degree of QT lengthening. This is unlikely, however, since clofilium, which produces a marked lengthening of cardiac repolarization, has a negligible effect on VPC suppression.[15]

Therefore, studies with newer pure class III agents (e.g., sematilide, UK 68,798 and E-4031), which have the lone property of lengthening the action potential duration with a corresponding change in refractoriness, will be necessary to resolve the issue. For the present, it may be reasonable to conclude that different class III agents may have varying potencies for VPC suppression because of associated properties. For example, in the case of sotalol, its antisympathetic activity is clearly important; in the case of amiodarone, the potent antiectopic actions, increasing as they do as a function of time, might be related not only to its associated antiadrenergic and class I electrophysiologic actions but possibly also to its property of tissue-specific thyroid hormone antagonism.[16]

It also seems that the actual length of the QT interval may not equate well with overall antiarrhythmic efficacy. One might expect a spectrum of antiarrhythmic efficacy for a given degree of QT lengthening by a number of class III agents. For example, ketanserin, N-acetylprocainamide and clofilium produce varying degrees (mild to considerable) of QT prolongation; they are relatively weak antiarrhythmic agents and have little or no suppressant effect on VPCs. In contrast, sotalol and amiodarone, which also produce mild to considerable QT lengthening relative to dose and duration of therapy, are potent antiectopic and antifibrillatory agents.[2] As discussed by Nademanee and Singh,[17] sotalol is effective in controlling resistant ventricular tachycardia and fibrillation. The drug is at least as potent as procainamide in suppressing ventricular tachycardia inducible by programmed electrical stimulation; some data suggest that sotalol might be more potent in this regard when compared with most of the conventional class I antiarrhythmic agents. Whether such a difference would pass the test of more rigorous controlled, comparative studies remains uncertain. The potency of a pure class III agent in suppressing ventricular tachycardia and fibrillation inducible by programmed electrical stimulation of the heart also remains speculative. Controlled clinical trials with agents that exert a relatively pure effect on repolarization and refractoriness will clearly be important in delineating the role of class III effects in mediating the antifibrillatory actions of these compounds.

d-SOTALOL AND CLASS III ANTIARRHYTHMIC ACTIONS: SIGNIFICANCE OF SYMPATHETIC INHIBITION

As indicated elsewhere,[18] the levo- and the dextroisomers of sotalol exert identical electrophysiologic actions on cardiac muscle, except for those effects mediated via competition for β receptors. In this regard, the dextroisomer (d-sotalol) is about 50-fold less active. Thus, d-sotalol has little effect on AV nodal conduction and refractoriness; it also has a much less bradycardic response than l-sotalol. The electrophysiologic profile of d-sotalol has been characterized in humans. It is similar to that in experimental animals and in cellular preparations. However, there are limited data on the comparative effects of the dextroisomer relative to the antiarrhythmic actions of dl-sotalol in humans.

Extensive clinical experience with dl-sotalol reviewed in this symposium has identified 3 potential practical advantages of d-sotalol when compared with the racemate (dl-sotalol). First, the relative absence of the β-blocking effect even at high doses is likely to minimize those adverse effects directly related to the blocking of adrenergic receptors. Second, the lack of β-blocking effects will lead to a corresponding reduction in the incidence and severity of heart failure, especially in patients whose ventricular performance depends critically on augmented sympathetic drive. Third, a less pronounced bradycardic effect, at least on theoretical grounds, is likely to be associated with a lower incidence of torsades de pointes, which occur in approximately 5% of patients given dl-sotalol. These features are clearly desirable. Their precise importance, however, can be gauged only by the comparative efficacy of d- and dl-sotalol in ventricular and supraventricular tachyarrhythmias relative to their proarrhythmic effects, especially the comparative incidence of torsades de pointes.

Nevertheless, there are reasons to believe that, at least as far as the issue of efficacy is concerned, it is unlikely that d-sotalol will be found to be as effective as dl-sotalol. Many lines of clinical and experimental data emphasize the significance of the adrenergic nervous system in mediating the genesis of life-threatening ventricular arrhythmias and the salutary effects of sympathetic antagonism in their control.[19] In recent years, β blockers have been the only class of agents that have been shown in controlled trials to reduce the incidence of sudden death in survivors of acute myocardial infarction,[20] an effect that is quantitatively correlated with heart rate reduction.[21] This emphasizes that the degree of β blockade is the crucial factor. It is known that both left stellate ganglionectomy and β blockade have been strikingly superior to no treatment or conventional treatment in preventing ventricular fibrillation in the hereditary long QT-interval syndromes.[22] Furthermore, there are emerging data that the benzofuran derivative amiodarone, which has a significant antiadrenergic effect acutely and chronically, has a beneficial effect in the survivors of acute myocardial

infarction who have VPCs documented on Holter monitoring.[23] Data documenting the value of amiodarone in patients with resistant symptomatic sustained ventricular arrhythmias and in survivors of sudden cardiac death in uncontrolled trials are also increasing.[14]

These data, interpreted in light of the extensive experimental studies that have documented the reduced probability of ventricular fibrillation by sympathetic inhibition, suggest that d-sotalol is unlikely to be as effective as dl-sotalol in life-threatening ventricular arrhythmias. Again, it will be crucial to compare the effects not only of d-sotalol but also of the pure class III agents with those of dl-sotalol and amiodarone in patients with symptomatic sustained ventricular tachycardia and in survivors of sudden cardiac death.

CLASS III ANTIARRHYTHMIC ACTIONS AND THE INCIDENCE OF TORSADES DE POINTES

The most specific and predictable proarrhythmic effect of drugs that lengthen cardiac repolarization is the electrocardiographic syndrome of torsades de pointes. This should be distinguished from the rapid and often incessant ventricular tachycardia that occurs in the wake of therapy with drugs that markedly delay conduction and that is often difficult to reverse or control. The latter proarrhythmic effect is particularly exemplified by class IC agents such as flecainide and encainide.[24] In contrast, torsades de pointes can often be reversed promptly and appear to be uncommonly associated with the development of ventricular fibrillation unless the patient is treated with drugs or interventions that further prolong cardiac repolarization. Therefore, it is important to identify the situations under which prolonged cardiac repolarization becomes the substrate for the development of torsades de pointes.

In recent years, a number of observations on the clinical significance of drug-induced lengthening of the QT interval have been made.[14] First, it is known that the relation is not linear between the degree of lengthening of the QT interval and the development of torsades de pointes. For example, a modest lengthening of the QT interval with quinidine may lead to the development of torsades de pointes, whereas a profound increase is rarely associated with the arrhythmia in the case of amiodarone. Second, for a given degree of QT lengthening produced by a variety of drugs, the incidence of torsades de pointes varies from one compound to the next. Third, there are several instances of QT prolongation in clinical situations (e.g., hypocalcemia and hypothyroidism) in which torsades de pointes or any other form of tachyarrhythmias are exceedingly rare. Finally, there is now compelling evidence[14] that lengthening the QT interval, induced by a number of cardioactive compounds (e.g., amiodarone and sotalol), constitutes a discrete antiarrhythmic and antifibrillatory mechanism, which was suggested many years ago.[1,12]

How does one reconcile these 2 seemingly paradoxic but experimentally and clinically well-supported observations? Clearly, as indicated elsewhere,[2] prolonging the QT interval must merely provide the substrate for the development of either an antiarrhythmic effect with a "modulated" lengthening of the effective refractory period (the so-called class III action exhibited by a number of compounds) or a proarrhythmic effect (torsades) when a set of associated features (e.g., hypokalemia, bradycardia and possibly delayed conduction) alters membrane stability over the plateau range of the action potential, thus leading to oscillations in the form of early afterdepolarizations. Such an electropharmacologic framework appears to be consistent with the clinical observation that different agents that prolong the QT interval of the surface electrocardiogram exhibit a variable incidence of torsades de pointes.

The difference in the propensity of various QT-prolonging agents or pathophysiologic states to induce torsades de pointes is of practical and theoretical importance. It may provide important insights regarding the underlying mechanisms of the arrhythmia. For example, in the case of hypocalcemia and hypothyroidism, torsades are rare unless there is associated severe hypokalemia.[25] Similarly, torsades de pointes occur infrequently[26] with amiodarone therapy, even though the drug markedly prolongs the QT interval (often over 600 ms) accompanied by pronounced bradycardia.[16] The reason for this is not clear, but preliminary data recently reported by Takanaka and Singh[27] suggested that it may be related to the associated calcium-channel blocking effects of amiodarone inhibiting the propensity for the development of early afterdepolarizations. In this context, it is interesting that in hyperthyroidism, the magnitude of the slow inward calcium current increases, and the converse is true in hypothyroidism[28]; the electrophysiologic effects of hypothyroidism closely resemble those of chronic amiodarone administration.[29]

Available evidence indicates that, at least so far as the effects of amiodarone on repolarization are concerned, such effects may be linked to drug-induced inhibition of T_3 action at the site of the myocardial nuclear receptor.[16]

If this were the case, one may draw 2 possible conclusions: First, the effects of amiodarone on repolarization, as in the case of hypothyroidism,[16,29] will be homogeneous from cell to cell, with little or no dispersion of refractoriness. This will lead to a reduced probability of focal reexcitation. Second, because the magnitude of the slow inward current is greatly diminished in the settings of both chronic amiodarone treatment[16] and in hypothyroidism,[28] the likelihood of torsades de pointes due to the development of calcium-mediated afterdepolarizations is correspondingly reduced. In both instances, torsades de pointes has been reported in cases of associated hypokalemia, indicating that electrolyte derangements (hypokalemia or hypomagnesemia) may at least partly nullify or reverse the protective effects of slow-channel block against the development of torsades de pointes.

This is consistent with the observations in the case of bepridil, a calcium channel blocker that significantly lengthens the QT interval. Most cases of torsades associated with the use of this drug have occurred in patients with reasonably severe hypokalemia.[30] However, if it can be established that most cases of torsades de pointes result from slow calcium channel mediated early afterdepolarizations, it is possible that a combination of a class III

antiarrhythmic agent with calcium antagonists (such as verapamil, diltiazem or the dihydropyridines) may prevent the development of torsades de pointes. In the meantime, attention is focused on sotalol as an effective class III antiarrhythmic compound for the control of ventricular and supraventricular tachyarrhythmias, which have a low propensity for inducing torsades.

FUTURE PROSPECTS AND CONCLUSIONS

Controlling arrhythmias by prolonging cardiac repolarization now appears to be an established therapeutic principle. Lengthening of repolarization in any cardiac tissue leads to a corresponding increase in the refractory period, which reduces the number of impulses the tissue can sustain per unit time, an effect that will reduce the probability of fibrillation. In the working myocardium, such as atrial and ventricular cells, prolonging the action potential will produce a positive inotropic action; this is obviously important in an antiarrhythmic agent for use in patients with impaired hemodynamic function. The overall properties of an agent that exerts its principal action by lengthening repolarization—the so-called class III mechanism—were first exemplified by sotalol, which has the additional property of blocking β receptors.

The electropharmacologic properties of sotalol, amiodarone and other class III antiarrhythmic agents indicate that lengthening cardiac repolarization merely provides the substrate for a potent and broad-spectrum antiarrhythmic action as well as for a well-defined proarrhythmic effect in the form of torsades de pointes. Which of these effects predominates during a particular clinical situation depends not only on the associated pharmacologic properties of the compound but also on the clinical setting. There does not appear to be a sound electrophysiologic rationale for pure class III agents to suppress VPCs and supraventricular contractions; the antifibrillatory actions of these drugs are likely to dominate their clinical effects. Their effects on the sinus node are complex, and it is not clear to what extent the class III effects in the sinus node might contribute to slowing of heart rate seen with some agents.

The varying potencies of different class III agents for controlling cardiac arrhythmias and their differing proclivities to induce torsades de pointes for a given degree of QT lengthening are not explained by known electrophysiologic properties. These differences, however, are practically and theoretically important. The availability of the patch-clamp and whole-cell clamp techniques[31] in cells isolated from all parts of the heart may permit studies to delineate the mechanisms underlying these differences in terms of structure-activity relations and individual ionic currents mediating repolarization and depolarization. Such studies may provide the basis for the essential links between the antifibrillatory and proarrhythmic correlates of prolonged cardiac repolarization.

REFERENCES

1. Singh BN, Vaughan Williams EM. A third class of antiarrhythmic action. Effects on atrial and ventricular intracellular potentials and other pharmacologic actions on cardiac muscle of MJ1999 and AH 3474. *Br J Pharmacol 1970;39:675–685.*

2. Singh BN. When is QT prolongation anti-arrhythmic and when is it proarrhythmic? *Am J Cardiol 1989;63:867–869.*

3. Senges J, Lengfelder W, Jauernig R, Czyfan E, Brachmann J, Rizos I, Cobbe S, Kubler W. Electrophysiologic testing of therapy with sotalol for sustained ventricular tachycardia. *Circulation 1984;69:577–583.*

4. Nademanee K, Feld G, Hendrickson JA, Singh PN, Singh BN. Electrophysiologic and antiarrhythmic effects of sotalol in patients with life-threatening ventricular tachyarrhythmias. *Circulation 1985;72:555–563.*

5. Carmeliet E. Electrophysiologic and voltage clamp analysis of the effects of sotalol on isolated cardiac muscle and Purkinje fibers. *J Pharmacol Ther 1985;232:817–825.*

6. Allessie MA, Bonke FIM. Atrial arrhythmias: basic concepts. In: Mandel WJ, ed. Arrhythmias: Their Mechanisms, Diagnosis and Management. *Philadelphia: JB Lippincott, 1987;186–207.*

7. Lynch JJ, Wilber DJ, Montgomery DG, Tsieh TM, Patterson E, Luchessi BR. Anti-arrhythmic antifibrillatory actions of the levo- and dextro-rotatory isomers of sotalol. *J Cardiovasc Pharmacol 1984;6:1132–1141.*

8. Rowland E. The clinical electrophysiological effects of d-sotalol—a new Class III antiarrhythmic drug (abstr). *JACC 1985;5:498.*

9. Deedwania PK. Suppressant effects of conventional beta-blockers and sotalol on complex and repetitive ventricular premature complexes. *Am J Cardiol 1990;65:43A–50A.*

10. Nademanee K, Lockhart E, Pruitt C, Singh BN. Cardiac electrophysiologic effects of intravenous ketanserin in humans. *J Cardiovasc Pharmacol 1987; 10:suppl 3:S81–S84.*

11. Zehender M, Meinertz T, Hohnloser S, Geibel A, Hartung J, Just H, the Multicenter Research Group. Incidence and clinical relevance of QT-prolongation caused by ketanserin—a new selective serotonin antagonist. *Am J Cardiol 1989;63:826–832.*

12. Singh BN, Vaughan Williams EM. The effect of amiodarone, a new anti-anginal drug, on cardiac muscle. *Br J Pharmacol 1970;39:357–367.*

13. Singh BN, Hauswirth O. Comparative mechanisms of action of antiarrhythmic drugs. *Am Heart J 1974;87:367–377.*

14. Singh BN, ed. Control of Cardiac Arrhythmias by Lengthening Repolarization. *Mount Kisco, NY: Futura Publishing, 1988;1–577.*

15. Steinberg MI, Lindstrom TD, Fasola AF. Clofilium. In: Scriabine A, ed. New Drugs Annual: Cardiovascular Drugs. Vol. 2. *New York: Raven Press, 1984:103–123.*

16. Singh BN. Amiodarone: historical development and pharmacologic profile. *Am Heart J 1983;106:788–797.*

17. Nademanee N, Singh BN. Effects of sotalol on ventricular tachycardia and fibrillation produced by programmed electrical stimulation: comparison with other antiarrhythmic agents. *Am J Cardiol 1990;65:53A–57A.*

18. Kato R, Yabek S, Ikeda N, Kannan R, Singh BN. Electrophysiologic effects of dextro- and levo-isomers of sotalol in isolated cardiac muscle and their in vivo pharmacokinetics. *JACC 1986;7:116–125.*

19. Jewitt DE, Singh BN. Beta-adrenergic blockade in acute myocardial infarction. In: Meltzer LE, Dunning AJ, eds. Textbook of Coronary Care. *Amsterdam: Excerpta Medica, 1974;282–305.*

20. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta-blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis 1985;27:335–371.*

21. Kjekshus J. Heart rate reduction—a mechanism of benefit? *Br Heart J 1985;8:suppl:115–122.*

22. Schwartz PH. Idiopathic long QT syndrome: progress and questions. *Am Heart J 1985;109:399–405.*

23. Burkart F, Pfisterer M, Kiowski W, Burckhardt D, Follath F. Improved survival in patients with asymptomatic ventricular arrhythmias after myocardial infarction with amiodarone: a randomized controlled trial. *Circulation 1989; in press.*

24. Singh BN. Editorial: Controlling cardiac arrhythmias: to delay conduction or to prolong refractoriness. *Cardiovasc Drugs Ther 1989; in press.*

25. Fredlund BD, Olsson SB. Long QT interval and ventricular tachycardia of "torsade de pointes" type in hypothroidism. *Acta Med Scand 1980;213:213–218.*

26. Rakita L, Mostow ND. Side effect profile of amiodarone and approaches to optimal dosing. In: Singh BN, ed. Control of Cardiac Arrhythmias by Lengthening Repolarization. *Mt. Kisco, NY: Futura Publishing, 1988;509–541.*

27. Takanaka C, Singh BN. Barium-induced non-driven action potentials as a model of triggered automaticity and early afterdepolarizations: differing effects of amiodarone and quinidine and significance of slow channel activity *JACC 1989; in press.*

28. Binah O, Bernstein I, Gilat E. Effects of thyroid hormone on the action potential and membrane currents of guinea pig ventricular myocytes. *Pflugers Arch 1987;409:214–216.*

29. Freedberg AS, Papp GJ, Vaughan Williams EM. The effects of altered thyroid state on atrial intracellular potentials. *J Physiol (Lond) 1970;207:357–368.*

30. Manouvrier J, Sagot M, Carson C, Vasklamm G, Leroy R, Reade R, Dacloux G. Nine cases of torsades de pointes with bepridil administration. *Am Heart J 1986;5:1005–1007.*

31. Nobel DJ, Powell T, eds. Electrophysiology of Single Cardiac Cells. *London: Academic Press, 1987;1–247.*

13.12.90

The American Journal of Cardiology

CALCUTTA CENTRAL LIBRARY UNIVERSITY

JANUARY 16, 1990

A Symposium: The Cardiac Arrhythmia Suppression Trial — Does It Alter Our Concepts of and Approaches to Ventricular Arrhythmias?

GUEST EDITOR:
Craig M. Pratt, MD
Associate Professor of Medicine
Director, Clinical Cardiology Research
Baylor College of Medicine
Director, Coronary Care Unit
The Methodist Hospital
Houston, Texas

A YORKE MEDICAL JOURNAL/CAHNERS PUBLISHING COMPANY

The American Journal of Cardiology

JANUARY 16, 1990 VOL. 65 NO. 4

A Symposium: The Cardiac Arrhythmia Suppression Trial—Does It Alter Our Concepts of and Approaches to Ventricular Arrhythmias?

GUEST EDITOR:

Craig M. Pratt, MD
Associate Professor of Medicine
Director, Clinical Cardiology Research
Baylor College of Medicine
Director, Coronary Care Unit
The Methodist Hospital
Houston, Texas

This symposium was held on August 9, 1989, in The Woodlands, Texas, and was supported by an educational grant from Parke-Davis.

EDITOR-IN-CHIEF
William C. Roberts, MD

MANAGING EDITOR, SPECIAL PROJECTS
Judith Wagner

PUBLISHER, SPECIAL PROJECTS
Kenton T. Finch

PRODUCTION EDITOR
Vicky Weisman

PROOF EDITOR
Mary Crowell

THE AMERICAN JOURNAL OF CARDIOLOGY.® (ISSN 0002-9149) January 16, 1990, Vol. 65, No. 4 (USPS: 505–750).

Member, American Business Press, Inc. and Audit Bureau of Circulations. Published 4 times in January, February, June, July, September and October, 3 times in March, April, May, August and November, and 2 times in December, by The Cahners Publishing Company, a Division of Reed Publishing USA, 275 Washington St., Newton, MA 02158-1630. Terrence M. McDermott, President; Jerry D. Neth, Vice President/Publishing Operations; J.J. Walsh, Financial Vice President/Magazine Division; Thomas J. Dellamaria, Vice President/Production and Manufacturing.

SUBSCRIPTIONS: Solicited only from cardiologists and other physicians. Publisher reserves the right to refuse unqualified subscribers. Subscribers agree that no article or any part thereof published in any editions of the American Journal of Cardiology received under this subscription agreement may be copied, recorded or reproduced in any form or by any means, electronic or mechanical, including, among other things, photocopying or the storing of part or all of such articles on any information retrieval system, without the written permission of the Publisher. Address correspondence regarding subscriptions and changes of address to: THE AMERICAN JOURNAL OF CARDIOLOGY, 44 Cook Street, Denver, Colorado 80206-5800 (1-800-327-9021). Please include your zip code and, in case of change of address, copy of old address label. Changes of address must reach the Journal one month preceding month of issue. Single copy price: Regular issues $10.00; Symposium and special issues $12.00. Subscription rate for individuals in field of publication: United States 1 year $66, 2 years $112, 3 years $158; Canada and all other countries 1 year $105, 2 years $178, 3 years $252; Residents and Medical Students: United States 1 year $33; Canada & all other countries 1 year $85. Institutions: United States 1 year $95, 2 years $162, 3 years $228; Canada & all other countries 1 year $125, 2 years $213, 3 years $300. Air Mail available at additional charge of $150 per year. The Journal is not responsible for replacing missing issues unless the Circulation Department is notified of nonreceipt within 3 months of issue date.

Second class postage paid at Denver, CO, and at additional mailing office. Printed in U.S.A. Trademark™ in U.S. Patent Office. © Copyright 1990 by Reed Publishing USA: Saul Goldweitz, Chairman; Ronald G. Segel, President and Chief Executive Officer. All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording or by any information storage retrieval system, without permission of the copyright owner. Prices on bulk reprints of articles available on request.

The Publisher assumes no liability for any material published in the Journal. All statements are the responsibility of the authors.

MANUSCRIPTS: Address all manuscripts to William C. Roberts, MD, Editor-in-Chief, the American Journal of Cardiology, 7960 Old Georgetown Road, Suite 2C, Bethesda, Maryland 20814.

POSTMASTER: Send address changes to: The American Journal of Cardiology, 44 Cook Street, Denver, Colorado 80206-5800.

Cahners Publishing Company, A Division of Reed Publishing USA ◻ Specialized Business Magazines for Building & Construction ◻ Manufacturing ◻ Foodservice & Lodging ◻ Electronics & Computers ◻ Interior Design ◻ Printing ◻ Publishing ◻ Industrial Research & Technology ◻ Health Care ◻ Entertainment.

CALCU CENTRAL LIBRARY UNIVERSITY

Publisher's Note

The opinions expressed in this presentation are those of the panelists and are not attributable to the sponsor or the publisher, editor, or editorial board of The American Journal of Cardiology. Clinical judgment must guide each physician in weighing the benefits of treatment against the risk of toxicity. References made in the articles may indicate uses of drugs at dosages, for periods of time, and in combinations not included in the current prescribing information.

Editor's suggestion: The symposium issues for a full year should be bound together separately from the regular issues.

CONTENTS

The American Journal of Cardiology

JANUARY 16, 1990 VOL. 65 NO. 4

A SYMPOSIUM: THE CARDIAC ARRHYTHMIA SUPPRESSION TRIAL — DOES IT ALTER OUR CONCEPTS OF AND APPROACHES TO VENTRICULAR ARRHYTHMIAS?

1B
Introduction: The Aftermath of the CAST — A Reconsideration of Traditional Concepts
Craig M. Pratt

3B
The AJC and Television: A Logical Marriage
Vincent E. Friedewald, Jr. and William C. Roberts

4B
Sudden Arrhythmic Cardiac Death — Mechanisms, Resuscitation and Classification: The Seattle Perspective
H. Leon Greene

13B
Sudden Cardiac Death: A Diversity of Causes with Focus on Atherosclerotic Coronary Artery Disease
William C. Roberts

20B
The Cardiac Arrhythmia Suppression Trial: Background, Interim Results and Implications
Craig M. Pratt and Lemuel A. Moye

30B
A Perspective on Ventricular Arrhythmias: Patient Assessment for Therapy and Outcome
Albert L. Waldo, Richard W. Henthorn, and Mark D. Carlson

36B
Clinical Implications of New Studies in the Treatment of Benign, Potentially Malignant and Malignant Ventricular Arrhythmias
Jeffrey L. Anderson

The American Journal of Cardiology

Introduction: The Aftermath of the CAST—A Reconsideration of Traditional Concepts

Craig M. Pratt, MD

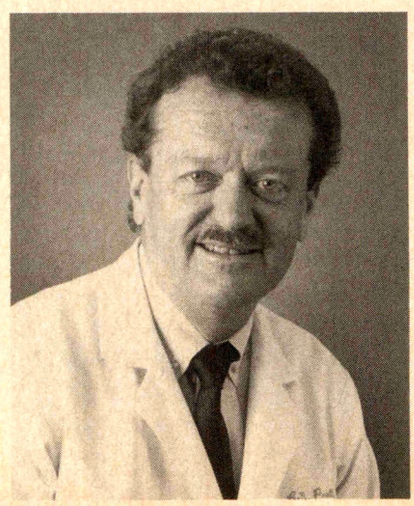
The intent of the Cardiac Arrhythmia Suppression Trial (CAST) was to test the hypothesis that suppression of ventricular arrhythmias in survivors of myocardial infarction would reduce arrhythmic death risk.[1] The alarming discovery that patients in the CAST taking encainide and flecainide had a 3.6-fold increase in arrhythmic death compared with their placebo group has resulted in a reevaluation of our concepts regarding the appropriate use of antiarrhythmic drugs. It was timely that the results of the CAST were closely preceded by an article from Hine et al.[2] They reported on the use of antiarrhythmic agents in the United States, which is increasing far out of proportion to changes in the size of the United States population. In fact, from 1970 to 1986, Hine et al estimated that antiarrhythmic drug use increased from 3.8 to 11.5 million new prescriptions annually. It is widely held by pharmaceutical companies that 40 to 50% of these prescriptions are for the treatment of ventricular arrhythmias.

While it is inevitable that attempts will be made to extrapolate these observations to other antiarrhythmic drugs and other patient populations we should be cautious. However, given the magnitude of the proarrhythmic effect of encainide and flecainide in the CAST, we should ponder the wisdom of these millions of prescriptions for the treatment of ventricular arrhythmias. This symposium provides state-of-the-art information about arrhythmic death presented in a cardiology journal. Communication of this information to internists, family practice physicians and general practitioners is very important, as they are responsible for over two-thirds of the antiarrhythmic drug prescriptions written in this country.[2] To achieve this goal, a 4-part video series summarizing the symposium has been broadcast on Lifetime Medical Television®.

In the CAST, both flecainide and encainide were effective suppressors of ventricular premature complexes; yet they turned out to be proarrhythmic, reminding us all that what seems reasonable and desirable is not necessarily good for patients. Greene begins this symposium with a review of the invaluable observations of sudden death made from years of study of the Seattle emergency medical care system (Medic I). He documents that most of the patients with arrhythmic death have sustained ventricular tachycardia or ventricular fibrillation, or both, at the time paramedics arrive. Those lucky enough to be resuscitated are usually found to have myocardial scarring and atherosclerotic coronary artery disease.

Roberts reviews the pathology of arrhythmic death victims at necropsy. He points out that there are many causes of sudden death, but the focus of the article is on detailed observations of the pathology of the coronary arteries. Even in patients without a history of myocardial infarction, myocardial scarring is frequently seen and is associated with extensive, diffuse coronary atherosclerosis. Roberts reminds us that clinical attention to reducing patients' cardiovascular risk factors, especially the reduction of their serum cholesterol levels, should be a productive strategy; primary prevention should not be ignored.

In my analysis of the CAST, I have reviewed the state of knowledge available before the initiation of that trial. A pilot study was clearly needed and therefore implemented, the Cardiac Arrhythmia Pilot Study (CAPS).



Craig M. Pratt, MD

From the Section of Cardiology, Department of Internal Medicine, Baylor College of Medicine, Houston, Texas.

Address for reprints: Craig M. Pratt, MD, Director, Coronary Care Unit, The Methodist Hospital, 6535 Fannin, MS F1001, Houston, Texas 77030.

The CAPS, a 502-patient study of survivors of myocardial infarction with ventricular premature complexes, provided valuable information to planning the CAST. The reasons it failed to reveal the serious proarrhythmic effects of encainide or flecainide are reviewed. In my discussion of the CAST, I focus on what I consider 2 fascinating issues: (1) Why was the placebo mortality in the CAST so extraordinarily low (approximately one-third the arrhythmic death rate seen in the CAPS)? (2) Is the arrhythmic death excess in the encainide/flecainide group a new type of proarrhythmia? This arrhythmic death excess defies traditional concepts of proarrhythmia caused by antiarrhythmic drugs both in terms of the timing (an excess of arrhythmic deaths occurred throughout the 10-month trial) and the patient population (this was a population defined as "potentially lethal," usually considered to have only modest proarrhythmic potential). These CAST results support the view that these arrhythmic deaths represent a new type of proarrhythmia, perhaps suggesting a unique mechanism. It may involve the interaction of ischemia, ventricular arrhythmia, and the electrophysiologic properties of specific antiarrhythmic drugs. There is already a foundation of knowledge of arrhythmic death from animal models suggesting that transient episodes of acute ischemia may convert "antiarrhythmic" drugs to "proarrhythmic" drugs. The demonstration of this phenomenon in animal infarct models has recently been emphasized by Ruskin.[3]

Waldo reviews our methods for arrhythmia assessment and emphasizes the limitations of Holter recordings when used alone to estimate arrhythmic death risk in certain populations. He suggests that a more extensive noninvasive evaluation (Holter recordings, signal-averaged electrocardiograms, exercise testing and assessment of left ventricular function) may provide a better profile from which to select the patients at high risk, either for invasive testing or consideration for antiarrhythmic therapy. Perhaps clinical information accumulated over the last decade should not be forgotten: Mortality risk in survivors of myocardial infarction is directly related to degree of left ventricular dysfunction, extent of ventricular arrhythmia, presence of myocardial ischemia and coronary anatomy. Our assessment and treatment strategies should encompass all these areas.

Anderson provides a review of our present concepts regarding the classification of ventricular arrhythmias and an overview of the available antiarrhythmic agents. He maintains that there is good evidence for using antiarrhythmic drugs in the lethal arrhythmia category. Perhaps the terms potentially malignant and potentially lethal, which describe patients like those in the CAST population, should be discarded, with a substitution of "prognostically significant" to lessen the likelihood of a reflex move to unnecessary or dangerous treatment with antiarrhythmic agents. Treatment algorithms for the various arrhythmia categories are provided.

The dramatic revelation of the CAST underscores its contribution to all clinicians. Previous reports on encainide and flecainide have evaluated the entire pharmaceutical databases of both drugs, in excess of 3,000 patients! Because of the unique design of the CAST, a patient population approximately one-fourth that size has revealed an enormous increase in arrhythmic death, previously undetected and, in patients like the ones in the CAST, essentially unsuspected. This emphasizes the power of a parallel placebo group. This unique proarrhythmia may represent a class action of IC agents alone, perhaps isolated to a specific population. We hope that future clinical trials will identify investigational and currently available (IA, IB) agents that have clinical benefit in populations similar to the CAST. The scientifically alluring possibility that IC agents have a unique proarrhythmic effect in the setting of acute ischemia should accelerate research efforts in animal models. The CAST affirms the necessity of, rationale for, and ethical validity in pursuing knowledge through randomized, placebo-controlled clinical trials.

The CAST results have wide implications for the development of new pharmaceutical agents. The currently conceived antiarrhythmic guidelines provided to the pharmaceutical industry by the Food and Drug Administration require reconstruction. Also, consideration must be given to the degree to which current antiarrhythmic drug labeling needs to be revised for other marketed antiarrhythmic drugs. In fact, the CAST results led to a special session of the Cardiovascular and Renal Drugs Advisory Board to the Food and Drug Administration on October 5 and 6, 1989. The question of how far to extrapolate these results is critical: Can they be applied to other type IC agents, to other electrophysiologic classes (IA, IB)? To what extent can these results be extrapolated to other types of patients? These questions are as important to clinical practice as they are to regulatory issues.

Although the results in the encainide/flecainide group of CAST do not "kill" the ventricular premature complex suppression hypothesis, neither do they provide any reassurance that this approach is worthwhile. The continuation of the CAST with additional antiarrhythmic agents (moricizine and possibly others) representing other electrophysiologic classes promises to provide further insight into the benefit of prophylactic antiarrhythmic therapy.

REFERENCES

1. CAST Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med 1989;321:406–412.*

2. Hine LK, Gross TP, Kennedy DL. Outpatient antiarrhythmic drug use from 1970 through 1986. *Arch Intern Med 1989;149:1524–1527.*

3. Ruskin JN. The Cardiac Arrhythmia Suppression Trial (CAST) (editorial). *N Engl J Med 1989;321:386–388.*

The AJC and Television: A Logical Marriage

Vincent E. Friedewald, Jr., MD, and William C. Roberts, MD

This supplement of *The American Journal of Cardiology* is important to the medical community, principally because it addresses one of the most important topics of our time: sudden cardiac death. In addition, this publication introduces a unique concept in which a traditional peer-review print supplement was developed in partnership with the medium of electronic communications; in this instance, television.

The Cardiac Arrhythmia Suppression Trial (CAST) is a landmark clinical trial in our quest to prevent sudden death. Therefore, the need to quickly and effectively disseminate information about the CAST to clinicians was critical. Numerous bulletins from the involved pharmaceutical companies were mailed directly to physicians, warning of the unexpected adverse results of 2 of the drugs evaluated in the study. These bulletins and an article published in *The New England Journal of Medicine* provided the first level of communication about the CAST results.

However, after any investigation, especially when the results are as dramatic and potentially far-reaching as the CAST, there remains the task of explaining the implications of the study to the practicing physician. With the support of Parke-Davis, we determined that this goal could be accomplished effectively by a combination of print and television media.

In August 1989, a group of the CAST investigators convened to discuss their study in a day-long forum. The entire session was videotaped and edited into four 30-minute programs for the "Milestones in Medicine" series on Lifetime Medical Television. The first of these programs was broadcast only 3 weeks after the original publication appeared in *The New England Journal of Medicine*, with subsequent programs appearing during September and October. Next, based on their presentations in the "Milestones in Medicine" television programs and the discussions that followed, each of these authorities wrote an article for this supplement. As a result, what was theoretically possible had become a reality: print and video had found a logical marriage.

In this era of television, computers, FAX machines, and other marvels of modern mass communications, has this experience taught us any lessons about how medical information should be disseminated? We believe it has. First, the initial publication of medical research in peer-review journals such as *The New England Journal of Medicine* is tried and proven to be best for both the medical profession and for the patients we serve. Despite the enormous impact of electronic communications on modern society, any temptation to circumvent this critical responsibility of the traditional print medium must be resisted. Second, the power and reach of television is so great that its ability to quickly and credibly disseminate information such as the CAST results cannot be ignored. And finally, print supplements are a valuable reference for those who desire a depth of discussion beyond the usual scope of video.

We are convinced that this AJC supplement, combined with the television programs from which it was derived, is an important step into the future of medical communications. Parke-Davis, one of the pioneers in supporting professional television, and a long-time supporter of the traditional print medium, is to be congratulated for its vision in supporting this effort. We encourage more sponsors to utilize this and other models of modern media techniques in order to achieve our common goal of imparting information in the most accurate and efficient means possible.

Sudden Arrhythmic Cardiac Death—Mechanisms, Resuscitation and Classification: The Seattle Perspective

H. Leon Greene, MD

Ventricular fibrillation (VF) is the first recorded arrhythmia in 75% of patients who have a sudden cardiovascular collapse. Rarely (1%) does sustained ventricular tachycardia (VT) alone cause collapse and unconsciousness. Whether all VF begins as VT is unknown.

Early application of cardiopulmonary resuscitation and rapid defibrillation are essential to ensure survival and satisfactory neurologic recovery. During the last 2 years in Seattle, the initial resuscitation rate for VF was 269 of 447 patients (60%), with 114 of 447 patients (26%) surviving long-term. Survivors of VF have a high overall risk of recurrent VF, with many univariate risk factors identified: evidence of poor left ventricular function (history of congestive heart failure, prior myocardial infarction [MI] or low ejection fraction), extensive coronary artery disease, absence of a new MI (either Q wave or non-Q wave) with VF, male gender, advanced age, complex or high-frequency ventricular ectopy on Holter recording, inducibility at electrophysiologic study, exercise-induced angina or hypotension, and smoking.

Classification of cardiac deaths as arrhythmic or nonarrhythmic is important in interpreting the therapeutic response. However, because many patients have chronic symptoms, timing of the onset of a new event is difficult. Furthermore, accurate timing of an event does not guarantee correct classification. Sudden death is not necessarily arrhythmic, nor is all arrhythmic death sudden. Total cardiac mortality may be a simpler and more relevant end point to measure the overall effect of antiarrhythmic therapy.

(Am J Cardiol 1990;65:4B–12B)

From the Division of Cardiology, Department of Medicine, Harborview Medical Center and University of Washington Medical Center, University of Washington, Seattle, Washington. This study was supported in part by Grants HL31472 and HL18805 and contracts N01-8C28004 and HL12474 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, and by grants from the American Heart Association, Washington Affiliate, the Medic I-Emergency Medical Services Foundation, the Jacob P. Glastra Memorial Fund, and the Harry H. Law Memorial Fund, Seattle, Washington.

Address for reprints: H. Leon Greene, MD, Harborview Medical Center, 325 Ninth Avenue (ZA-35), Seattle, Washington 98104.

Sudden arrhythmic cardiac death continues to be a major medical problem for which no solution has been found. Extensive resources and research have been directed toward identifying the causes of and treatments for this disorder. The ideal solution would be to prevent the diseases that cause the initial episode of cardiac arrest. Modest success has been obtained in resuscitating the victim after the first event, and major attention has been directed to evaluation and treatment of the survivor of an episode of out-of-hospital ventricular fibrillation (VF). It has been estimated that 200,000 to 600,000 persons in the United States succumb annually to a cardiac arrest,[1,2] although recent reports indicate that the death rates from coronary heart disease appear to be gradually decreasing.[3–5] Nevertheless, the problem of sudden arrhythmic cardiac death continues to have an enormous medical, economic and emotional impact in this country. This review will highlight some of the lessons learned from the experience in Seattle with resuscitation and evaluation of patients with aborted sudden cardiac death, and will discuss some of the problems of defining and classifying these events.

MECHANISMS AND ARRHYTHMIAS RESPONSIBLE FOR SUDDEN CARDIAC DEATH

Extensive epidemiologic data are available on patients who have an episode of cardiac arrest.[6–12] The typical Seattle patient is outlined in Table I. Most patients with coronary artery disease do not have an acute myocardial infarction (MI) during an episode of VF. Whereas 38% of patients will have evidence of myocardial necrosis by cardiac enzymes, in only 19% will Q waves compatible with a transmural MI develop.[6,8,12] Although an occasional patient will have hypokalemia, it is usually mild, and in very few patients is it likely to contribute substantially to the arrhythmia itself.[13]

The rhythm identified early in the course of sudden arrhythmic cardiac death is VF in 75%, asystole in 20% and electromechanical dissociation in 5%.[12,14] The frequency of asystole is usually directly proportional to the interval from collapse to first monitoring of the cardiac rhythm; a longer duration of collapse before monitoring is more likely to be associated with a "flat line."[6,10] Survival is directly related to the initial recorded rhythm (Table II). Whereas 25% of patients in Seattle survived long-term after a cardiac arrest in which VF was the first observed rhythm, only 1% of patients who were found

TABLE I Typical Survivor of Ventricular Fibrillation in Seattle

Male	83%
Age (years)	60 ± 12
Coronary artery disease	75%
History of cardiovascular disease	77%
Angina	38%
Congestive heart failure	23%
Prior myocardial infarction	45%
Hypertension	36%
Not taking antiarrhythmic drugs	89%
Not exercising	73%
No distinctive warning symptoms	70%
No acute Q-wave myocardial infarction	81%

Reproduced with permission from *Mod Med.*[11]

TABLE II Cardiac Arrest in Seattle (1971–1987): Long-Term Survival Rates

	Number of Patients	
	Initial Recorded Rhythm	Long-Term Survival
Ventricular fibrillation	3,893 (75%)	977 (25%)
Asystole	1,059 (20%)	13 (1%)
Electromechanical dissociation	247 (5%)	15 (6%)
Total	5,199 (100%)	1,005 (19%)

Adapted from *Ann Emerg Med.*[14]

with asystolic rhythm were long-term survivors, compared with 6% of patients with electromechanical dissociation.[14] Sustained ventricular tachycardia (VT) is seldom the first recorded rhythm in a patient who has experienced a clinical cardiac arrest, accounting for only 1% of all cardiac arrests in Seattle.[15] It is possible, however, that a cardiac arrest begins as a brief run of VT that rapidly degenerates to VF, leaving the patient with few or no premonitory symptoms or signs to suggest that the initial rhythm had been VT. If VF persists long enough the voltage may decrease, so that the first recorded rhythm appears to be asystole. In contrast, cases of VF spontaneously converting to asystole with a rare idioventricular escape beat have been reported.[14]

Extensive use of Holter ambulatory electrocardiographic recording over the past few years has allowed the cardiac rhythm to be observed in many patients who have had a cardiac arrest while wearing these devices.[16–21] However, a patient wearing a Holter recorder is frequently taking an antiarrhythmic drug, and the effects of such drugs must be considered when evaluating Holter recordings of patients who collapse. Likewise, patients who wear Holter recorders probably will have had symptoms that prompted the application of the recorder, and these patients may be selected from a different population than the average patient who has a sudden cardiac death without premonitory symptoms.

Nikolic et al[16] reported 6 cases of sudden cardiac death during which Holter recordings were available. Five of the 6 patients had VT and VF, and only 1 had a bradyarrhythmia. Three of these patients were taking antiarrhythmic medications at the time of their cardiac arrest (2 quinidine and 1 mexiletine). They reviewed an additional 15 cases from published reports and concluded that extensive myocardial disease was a common denominator for all cases. Most patients also had complex ventricular ectopy. Nine of 21 patients were taking an antiarrhythmic drug other than digitalis or propranolol.

Pratt et al[17] reported 15 patients with VF recorded during Holter monitoring. In all patients, VT initiated the VF, and the runs of VT were usually long and rapid. It is unclear how many of these patients were hospitalized. Twelve patients were taking digitalis and 5 were taking quinidine. Other factors that may have contributed to the arrhythmia were coronary artery disease, left ventricular dysfunction and left ventricular hypertrophy. No ST-segment changes were present to implicate ischemia as a causative factor. Similar findings have been noted by Panidis and Morganroth.[18]

Milner et al[20] reported 13 patients who had an in-hospital cardiac arrest during Holter electrocardiographic recording. All of these patients had previously experienced an episode of cardiac arrest or syncope. The investigators identified VT as the initiating event in 12 patients. One patient had bradycardia followed by VF. In this study, the VT degenerated to VF after a mean duration of 96 seconds. The initial VT rate was quite rapid, averaging over 200 beats/min. However, 10 of 13 patients were taking antiarrhythmic medications at the time of the cardiac arrest, distinctly different from the typical patient with out-of-hospital VF.

Most recently, 157 cases of fatal cardiac arrest that occurred while patients were wearing Holter recorders have been summarized by de Luna et al.[21] Primary VF was seen in 8%, VT degenerating to VF in 62%, and torsade de pointes in 13%. Bradycardias were the primary arrhythmia in only 17% of all cases. Antiarrhythmic drug use was common in these patients. Fifty-one percent of patients with VT, 69% with torsade, and 29% with bradycardia as the recorded terminal arrhythmia were taking antiarrhythmic drugs. The percentage of patients who were hospitalized at the time of the fatal arrhythmia is not clear.

Patients who sustain a cardiac arrest while wearing a Holter recorder may not be representative of the typical population of patients with VF. Frequently, such patients are taking antiarrhythmic drugs, have had prior symptoms, and are hospitalized and seriously ill with coexisting cardiac and noncardiac diseases. The recent findings of the Cardiac Arrhythmia Suppression Trial (CAST) suggest that some of these fatal events recorded on Holter monitoring may have been caused by the antiarrhythmic drugs themselves.[22]

ORGANIZATION OF SEATTLE'S EMERGENCY MEDICAL CARE SYSTEM

The emergency medical care system in Seattle, known locally as Medic I, is a tiered response system.[23–27] It is organized so that accessing the emergency care system via a 911 telephone call will initiate a response from

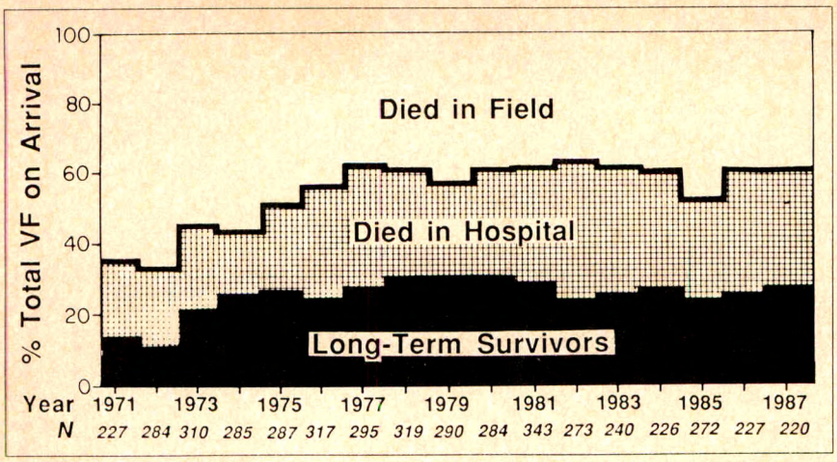


FIGURE 1. Success of resuscitation from out-of-hospital ventricular fibrillation (VF) in Seattle between 1971 and 1987. Recent overall success, defined as discharge from hospital neurologically intact, is 26%. N = number of cases of VF each year.

TABLE III Neurologic Outcomes of Cardiac Arrest

	With Bystander CPR (n = 36)	No Bystander CPR (n = 82)	p
Purposeful activity at admission	18/36 (50%)	5/82 (6%)	<0.001
Conscious by 24 hours	22/36 (61%)	7/82 (9%)	<0.001
Confused at discharge	1/27 (4%)	18/38 (47%)	<0.001
Vegetative state at discharge	0	3/38 (8%)	<0.001

CPR = cardiopulmonary resuscitation.
Reproduced with permission from *Ann NY Acad Sci.*[25]

personnel at the nearest available fire station, who will arrive by either a fire truck or an ambulance. The initial responders are emergency medical technicians trained in basic first aid and cardiopulmonary resuscitation (CPR). The average response time for this initial aid is 2.6 ± 1.7 minutes.[28] As soon as it is recognized that a serious cardiac emergency has occurred, often at the time of the initial 911 call, a more advanced paramedic unit is simultaneously dispatched to the scene. These paramedics have received over 1,600 hours of training, and are skillful in advanced life support, including endotracheal intubation, CPR, arrhythmia monitoring and treatment, defibrillation, and administration of cardiac drugs. When necessary, communication with a physician is available through a 2-way radio or by telephone. The average response time of the paramedic units is 6.0 ± 2.9 minutes.[28] Most patients who are successfully resuscitated are stabilized in the field, and it is uncommon for CPR to be ongoing while on route to the hospital.

Each year in Seattle, 200 to 300 persons have unexpected cardiovascular collapse and VF when found by the paramedics (Fig. 1).[14] A city-wide education program has resulted in more than 200,000 Seattle citizens being trained in the administration of CPR.[6] By 1980, 40% of resuscitations of cardiac arrest victims had been initiated by bystanders. Approximately 25,000 persons are trained in CPR annually.[25] With bystander-initiated CPR, first response of the emergency medical technicians in 2.9 minutes, and response of the paramedics in 6.0 minutes, the initial resuscitation rate is approximately 60% (133 of 220 for 1987). Patients who receive bystander CPR are more likely to have a good outcome, with 43% of patients surviving, compared with 21% of patients who do not receive this initial emergency measure. Likewise, the neurologic course after resuscitation is improved in those patients who receive bystander CPR (Table III).

On arrival of the first responding aid unit to victims of sudden collapse, the initial rhythm is usually VF. Early treatment of VF, most recently with automatic external defibrillators, has yielded an improved resuscitation rate.[15,29] Factors related to improved outcome are (1) a witnessed collapse, (2) a younger age, (3) higher amplitude VF, (4) a shorter response time for paramedics, and (5) initial treatment with the automatic external defibrillator.[15] Both the interval from collapse to onset of CPR and the duration of CPR necessary before the first external shock is administered are important (Fig. 2, Table IV).[14,30,31] Table IV also relates survival to the time from collapse to initiation of CPR and survival to the minutes of CPR before the first shock. Survival is best when CPR is initiated ≤3 minutes from collapse and when <6 minutes of CPR elapse before the first shock. Many patients are actually beginning to awaken, and some are even alert and oriented, at the time of admission to the hospital, some minutes after their cardiac arrest. In the Seattle experience, 81% of patients who received bystander CPR eventually regained consciousness, compared with 52% of patients who did not receive bystander CPR ($p < 0.004$). The improvement in hospital survival appears to be related to both a reduction in the incidence of cardiogenic shock (26 vs 8% with bystander CPR) and anoxic coma (22 vs 11% with bystander CPR).[14,24,25,28,30,31] In all, approximately 25% of the patients who are found to have VF will be discharged from the hospital alive and well.

In another population of patients from Seattle, a trial of high- and low-energy defibrillation was performed to detect any differences in overall outcome.[7] Both energy levels of defibrillation were equally successful in producing an organized rhythm after 1 or 2 shocks. Repeated shocks at the high energy level produced atrioventricular block in more patients (24% receiving 320 J vs 9% receiving 175 J, $p < 0.005$). Initial 175-J shocks were thus as

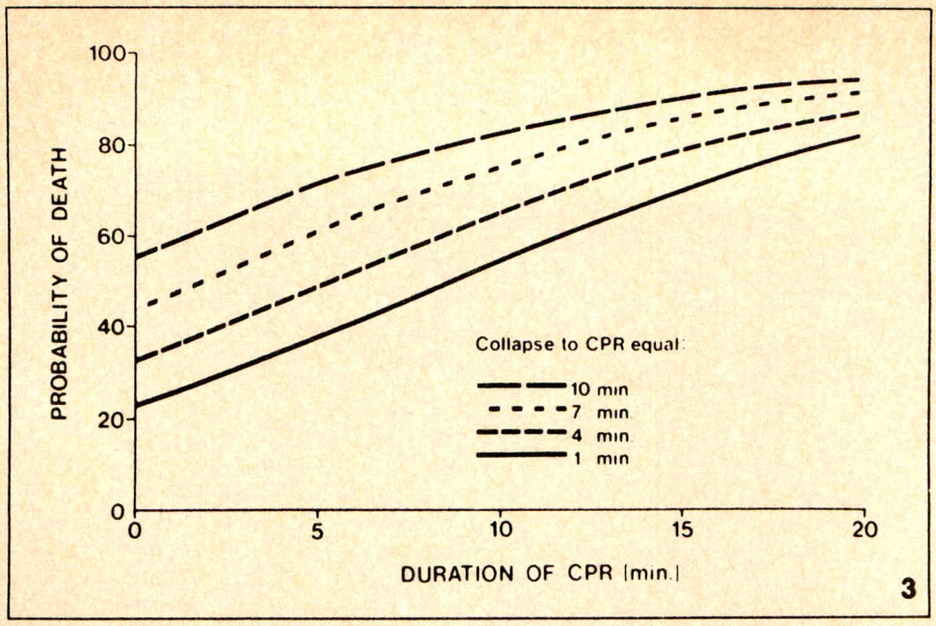


FIGURE 2. Mortality from cardiac arrest related to (1) time from collapse to onset of cardiopulmonary resuscitation (CPR) and (2) duration of CPR. Probability of death increases as both variables increase. (Reproduced with permission from *Ann Emerg Med.*[14])

safe and effective as higher energy shocks. Patients who survived hospitalization required fewer shocks than patients who succumbed during their hospital admission. Nearly 50% of patients who required only 1 shock were successfully resuscitated and ultimately discharged from the hospital, compared with <15% of patients who required ≥8 shocks to establish an organized rhythm.

LABORATORY FINDINGS AND RISK FACTORS FOR RECURRENT VENTRICULAR FIBRILLATION

Early studies from Seattle documented the high long-term subsequent mortality rate in patients who had been resuscitated from VF.[6,8–10,32] At the end of 1 year, 26% of patients had died, and at the end of 2 years, 38%. The presence of an acute Q-wave (transmural) MI developing at the time of the VF seemed to be protective against future events. In patients with new Q waves, the 1-year mortality was 0% and the 2-year mortality was 14%. In patients without new Q waves, 1-year mortality was 32% and 2-year mortality was 43% (Fig. 3). These findings support the concept of "primary" VF, in which the episode of cardiac arrest is not associated with a new Q-wave MI and for which the subsequent mortality is high, particularly the mortality from recurrent cardiac arrest. Patients who had enzymatic evidence of myocardial necrosis were at a lower risk than patients without enzyme elevations (Fig. 4). The mortality for patients with enzymatic evidence of myocardial necrosis was 14% at 1 year and 25% at 2 years, compared with patients without myocardial necrosis, in whom the mortality rate was 30% at 1 year and 47% at 2 years. Myocardial damage before the episode of VF, as evidenced by a history of a previous MI or a history of congestive heart failure, was also predictive of recurrent VF in follow-up. Other factors that are univariate predictors of recurrent cardiac arrest include evidence of abnormal left ventricular function,[33] extensive coronary artery disease,[34] complex or high-frequency ventricular ectopy on Holter recordings,[35] advanced age,[36] male gender,[32] exercise-provoked angina pectoris or hypotension (Table V),[37] and inducibility at electrophysiologic study.[38–43]

The mortality after resuscitation from VF is directly related to cardiovascular causes.[10] In 234 Seattle patients followed after resuscitation, 89 deaths occurred, 64 (72%) of which were sudden arrhythmic cardiac deaths.

TABLE IV Survival from Out-of-Hospital Ventricular Fibrillation

Minutes from Collapse to CPR	Minutes of CPR to First Shock			
	<6	7–12	>12	Total
≤3	23 (70%)	20 (44%)	1 (7%)	44/92 (48%)
>3	42 (39%)	13 (31%)	2 (22%)	57/159 (36%)
Total	65/141 (46%)	33/87 (38%)	3/23 (13%)	101/251 (40%)

CPR = cardiopulmonary resuscitation.
Reproduced with permission from *Ann Emerg Med.*[14]

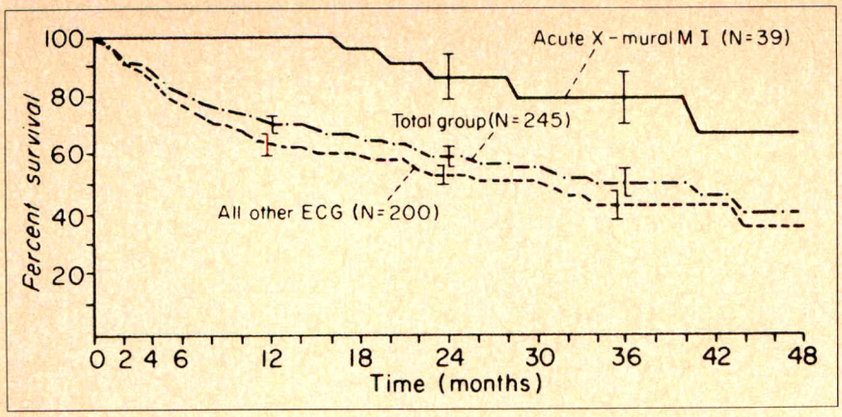


FIGURE 3. Long-term survival after ventricular fibrillation (VF); relation to Q-wave myocardial infarction (MI) at the time of VF. The development of such an infarction at the time of VF is a good prognostic sign for subsequent survival. X-mural MI = transmural (Q wave) myocardial infarction at the time of VF; ECG = electrocardiogram. (Reproduced with permission from *Circulation.*[12])

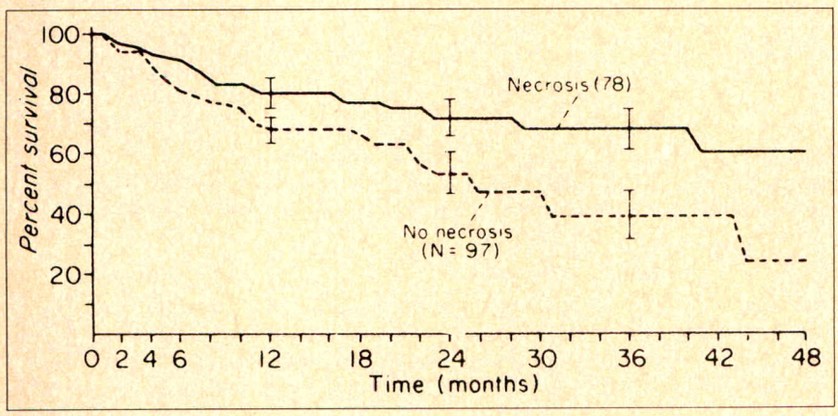


FIGURE 4. Long-term survival after ventricular fibrillation; relation to enzymatic evidence for myocardial damage. The elevation of myocardial enzymes is a good prognostic sign for subsequent survival. (Reproduced with permission from *Circulation.*[12])

The median time to recurrent cardiac arrest was 20 weeks from the original episode. These subsequent episodes of VF frequently were unheralded. Symptoms were infrequent, and patients were generally not exercising at the time of their recurrent episode of VF. Since these initial observations, cigarette smoking has emerged as another risk factor for recurrent cardiac arrest.[44] Cessation of smoking correlated with an improved survival rate. Recurrent cardiac arrests occurred in 19% of patients who had quit smoking, compared with 27% of patients at 3 years who had continued to smoke.

Electrocardiographic evaluation of survivors of out-of-hospital VF has shown that 30% of survivors have ventricular premature depolarizations on routine electrocardiograms, compared with only 13% of ambulatory post-MI patients ($p < 0.01$).[45] In addition, survivors of VF have more ST-segment abnormalities and QT prolongation than the control group. However, these electrocardiographic abnormalities are neither sensitive nor specific enough to identify patients at high risk of recurrent events. Although 24-hour Holter ambulatory recordings identified patients at risk of recurrent VF, ventricular premature depolarizations were frequent, occurring in 90% of patients.[35] Complex ventricular ectopic activity occurred more frequently in patients who had a subsequent event than in patients who remained free of recurrent arrhythmias (56 vs 28%, $p < 0.005$, specificity 72%, relative risk 2.3). However, only 67 of 144 patients (47%) in this study were not treated with an antiarrhythmic drug in long-term follow-up.

Although most episodes of VF do not occur with strenuous exertion, cardiac arrest occasionally may be precipitated by physical activity.[34,46] Although difficult to quantify, exercise appears to be an additional risk in the patient prone to ventricular arrhythmias. In 1 study,[37] 90 patients who had previously been resuscitated from a cardiac arrest (only 27% had experienced their prior VF in relation to physical activity) performed exercise tests. Paradoxically, more patients who experienced spontaneous VF at rest developed exertion-related arrhythmias on the treadmill than patients who had VF during exertion

TABLE V Univariate Predictors of Recurrent Cardiac Arrest in Resuscitated Survivors of Ventricular Fibrillation

Abnormal left ventricular function (low ejection fraction)[8,32,33]
Remote myocardial infarction
History of congestive heart failure
Extensive coronary artery disease[34]
No new Q-wave myocardial infarction with the VF[8,32]
Male gender[32]
Advanced age[36]
Exercise-induced angina or hypotension[37]
Complex ectopy on Holter monitoring[35]
Inducibility at electrophysiologic study[38–43]
Smoking[44]

VF = ventricular fibrillation

(52 vs 26%, $p < 0.05$). However, development of angina or inability to elevate the blood pressure with exercise predicted subsequent spontaneous cardiac arrest. Mortality at 2 and 4 years was 54 and 69%, respectively, in the patients with a treadmill test result positive for angina or exertion-related hypotension, compared with 26 and 42% in patients without this response. Thus, most patients in whom out-of-hospital cardiac arrest develops have not had their arrhythmia provoked by exertion, and the exercise test is a relatively poor technique for exposing ventricular electrical instability.

The degree of left ventricular dysfunction is the most powerful predictor of subsequent outcome in survivors of cardiac arrest.[32,33] Radionuclide ventriculography was performed to evaluate 154 survivors of out-of-hospital VF in Seattle. The mean left ventricular ejection fraction at rest was 0.40 ± 0.16. The response to exercise was even more abnormal, with only 3% of patients (3 of 91) able to increase their ejection fraction during exercise. During follow-up, 54 patients died, 42 suddenly. The most powerful predictor of outcome was the ejection fraction at rest, followed by arrhythmias on ambulatory Holter recording, history of congestive heart failure, and absence of a new Q-wave MI at the time of VF. Similarly, when 64 Seattle patients with coronary artery disease were evaluated with coronary angiography and left ventriculography, recurrent VF was more frequent in the group with 3-vessel disease, lower ejection fraction, and more severe abnormalities of regional left ventricular wall motion.[34]

Multivariate analysis of patients surviving cardiac arrest has identified 4 major factors that contribute to recurrence of cardiac arrest: (1) history of congestive heart failure, (2) history of prior MI before the episode of VF, (3) absence of an acute Q-wave MI at the time of VF, and (4) male gender. Accurate prognostic indexes can be constructed from knowledge of these basic data alone.[32]

PATIENTS WITH VENTRICULAR FIBRILLATION VERSUS THOSE WITH RECURRENT SUSTAINED VENTRICULAR TACHYCARDIA

The electrophysiologic substrate for ventricular arrhythmias may be different in patients with VF compared to those with recurrent sustained VT. Most reports dealing with "malignant" ventricular arrhythmias primarily report patients who have had recurrent sustained VT. We have evaluated these 2 patient groups separately.

The signal-averaged electrocardiogram has been used as a noninvasive technique for identifying patients who are at risk of developing sustained VT or VF before the initial episode as well as those at risk for recurrent episodes. We evaluated 46 patients with documented VF and 25 patients with recurrent sustained VT (Table VI). Electrocardiographic late potentials occurred more often in patients with recurrent sustained VT (83%) than in patients with VF (50%, $p < 0.005$). Late potentials, which are thought to arise in or near scarred areas of myocardium and may correlate with areas of delayed conduction, are more likely to be seen in patients with ventricular aneurysms, extensive ventricular scarring, frequent remote MIs and low ejection fractions. Patients with extensive ventricular scarring may have a more stable VT reentrant circuit, allowing maintenance of a slow, morphologically uniform VT that is reasonably well tolerated. In contrast, patients with no late potentials may lack the established reentrant circuits and their ventricular arrhythmias may be more chaotic and rapid.

TABLE VI Signal-Averaged Electrocardiographic Late Potentials

	n	T40 (μV)	% Late Potentials
Ventricular tachycardia	25	16 ± 8	83% (21/25)
Ventricular fibrillation	46	26 ± 15	50% (23/46)
p		<0.005	<0.005

T40 = signal magnitude (root mean square) in terminal 40 ms of QRS.

TABLE VII Differences Between Patients with Sustained Ventricular Tachycardia and Ventricular Fibrillation

	VT (n = 35)	VF (n = 66)	p
Age (year)	64 ± 11	60 ± 12	NS
Male gender	91%	82%	NS
Prior myocardial infarction	30/31 (97%)	36/49 (73%)	<0.01
Ejection fraction	0.36 ± 0.11	0.41 ± 0.17	<0.05
Left ventricular aneurysm	19/29 (66%)	14/46 (30%)	<0.005

NS = not significant; VF = ventricular fibrillation; VT = ventricular tachycardia. Reproduced with permission from *JACC*.[48]

We also evaluated these 2 patient groups by invasive electrophysiologic testing and correlated the results of these tests with clinical, angiographic and electrocardiographic findings.[47] We evaluated 66 survivors of out-of-hospital cardiac arrest and 35 patients with hemodynamically well-tolerated sustained VT. The patients with recurrent sustained VT had a higher incidence of previous MI and left ventricular aneurysm and a lower ejection fraction than survivors of VF (Table VII). Electrophysiologic testing showed a slower, hemodynamically well-tolerated, monomorphic VT induced in patients with recurrent sustained VT. In contrast, patients with a history of VF were more frequently noninducible; but the arrhythmias, when induced, were more rapid, polymorphic, and more frequently degenerated to VF than arrhythmias induced in patients with recurrent sustained VT (Table VIII).

Inducibility of sustained ventricular arrhythmias with programmed electrophysiologic pacing techniques is less common in survivors of VF than in patients with recurrent sustained VT.[38–43,48] In our large cooperative study of 241 survivors of out-of-hospital VF from the University of Washington, University of Oregon and Stanford University, only 44% of VF patients had an inducible ventricular arrhythmia. At baseline drug-free electrophysiologic testing, VF was the only inducible arrhythmia in 39 patients (16%), sustained VT was inducible in 66 patients (27%), and no sustained arrhythmia was in-

TABLE VIII Electrophysiologic Differences Between Patients with Sustained Ventricular Tachycardia and Ventricular Fibrillation

	VT (n = 32)	VF (n = 59)	p
Arrhythmia induced			<0.002
None	6 (19%)	15 (25%)	
NSVT	3 (9%)	11 (19%)	
VT	22 (69%)	18 (30%)	
VF	1 (3%)	15 (25%)	
VT morphology			<0.0001
Monomorphic	22 (85%)	15 (34%)	
Polymorphic	4 (15%)	29 (66%)	
VT cycle length (ms)	300 ± 64	259 ± 47	<0.01
Termination			<0.05
Pacing	16 (70%)	13 (40%)	
DC cardioversion	7 (30%)	20 (60%)	

DC = direct current; NSVT = nonsustained ventricular tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia.
Reproduced with permission from *JACC.*[48]

ducible in 136 patients. Although VF is often considered to be a nonspecific finding at electrophysiologic testing, it may be important in patients in whom the clinical arrhythmia is VF. Recurrence of VF at follow-up was predicted by inducible VF at the time of the baseline drug-free study, suggesting that inducible VF in this specific patient population is a relevant finding.

The surgical outcome of patients with recurrent sustained VT also is different from the outcome in patients with a history of VF (Fig. 5).[49] The 2-year mortality is 18% in patients with a history of VT, 14% with a history of VF, and 30% with a history of both arrhythmias.

REFINING THE DEFINITION AND CLASSIFICATION OF CARDIAC DEATH

Observations on the results of therapy in patients with a history of VF may be influenced by the classification of subsequent events. The ultimate goal of antiarrhythmic drug therapy, arrhythmia surgery and device therapy is to prevent recurrent episodes of cardiac arrest caused by arrhythmias. Whereas these therapies would not be expected to alter mortality from other causes, such as cancer, these other causes of death generally are easy to identify. In contrast, it is frequently difficult, if not impossible, to separate arrhythmic from nonarrhythmic causes of cardiac death. The patient with cardiovascular disease frequently has chronic symptoms, and it is often difficult to tell if the patient's death was simply the result of gradual progression of these symptoms as the cardiac disease process itself worsens, or if an event occurred that could reasonably have been prevented by an effective antiarrhythmic therapy, whether it be drug, surgery or device.

Many studies have attempted to classify deaths primarily by timing.[50–60] It is common to classify deaths as "sudden" or "nonsudden" strictly on the basis of the timing of symptoms in relation to loss of consciousness. A patient who dies within 1 hour of the onset of new symptoms is often assumed to have had an arrhythmic death. It is quite possible, however, that patients could die within 1 hour from recurrent MI and cardiogenic shock without arrhythmia, from cardiac rupture, pulmonary emboli, or a number of other causes that could evolve quite rapidly. Conversely, some patients may have a relatively slow progression of symptoms, lasting more than 1 hour, but in which the terminal event is an arrhythmia. An example would be a patient who has a small recurrent MI, develops chest pain, and 2 hours later has an episode of VF, an electrical event that might have been prevented by an effective antiarrhythmic therapy.

All classification schemes to analyze cardiac deaths are cumbersome. Some investigators have used the term instantaneous death as the purest form of probable arrhythmic etiology, defining events that occur <5 minutes from the onset of symptoms.[56] Even with this restricted definition, patients could die from other causes within this very short time frame without an arrhythmia being a major contributor to the mechanism of death. A 1-hour criterion is less restrictive,[58] although other time-based definitions have been used to identify an arrhythmic etiology. In the Cardiac Arrhythmia Pilot Study (CAPS), the temporal association of symptoms with time of death resulted in a classification error rate of 27%.[61] In the CAPS, 3 arrhythmic deaths had a duration of symptoms lasting >1 hour, and 9 nonarrhythmic deaths occurred <1 hour from the onset of symptoms to death. Thus, 12 of

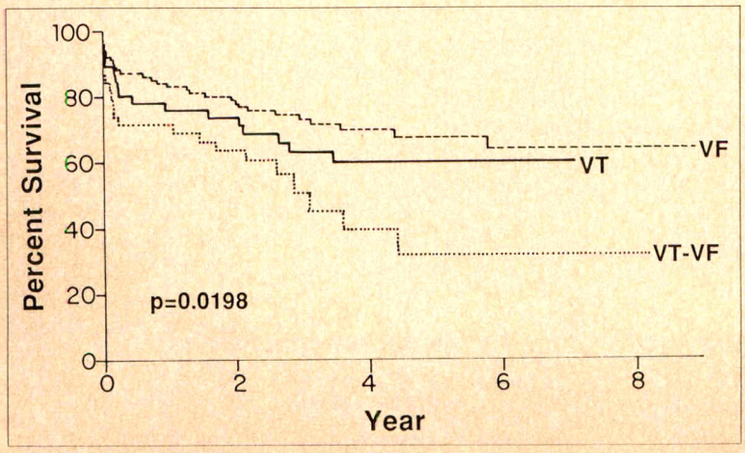


FIGURE 5. Long-term survival after surgical therapy for patients with ventricular fibrillation (VF), ventricular tachycardia (VT), or both arrhythmias. Patients with a history of both recurrent sustained VT and VF have the worst prognosis.

45 patients would have been misclassified using only a time-based definition, when the standard was the Events Committee review of all of the available data surrounding the deaths. Classification of a cardiac death as sudden or nonsudden using this 1-hour definition is therefore not equivalent to the classification of arrhythmic and nonarrhythmic. Similar difficulties have arisen in other large multicenter trials.[50–52,54] The classification of Hinkle and Thaler[53] is not as time-dependent as some of the other classification schemes, but it also is cumbersome. Using a strictly time-based definition, 23% of patients in their study would have been misclassified. Four of their nonarrhythmic deaths occurred in <1 hour, and 29 arrhythmic deaths were associated with symptoms lasting >1 hour.

Assessment of the mechanism of cardiac death requires that death caused by irreversible myocardial pump dysfunction be distinguished from death caused primarily by an electrical event. Although patients with end-stage congestive heart failure often have a terminal arrhythmia, they would not survive even if the arrhythmia could be prevented or terminated. Thus, classification of the cause of death as arrhythmic implies that the patient would have survived had the arrhythmia not occurred. However, "survived" implies a time frame. The CAPS Events Committee ultimately decided on an arbitrary criterion that the patient must have been able to survive for 4 months had the arrhythmia not occurred.[61] This definition, of course, is highly subjective and dependent on estimates from the investigator. Furthermore, it does not include any assessment of quality of life, which would be useful for a practical definition of arrhythmic death. Nevertheless, it is a functional classification that may have some utility. Therapy that will prolong life for only a few days or weeks may not be reasonable to administer. The physician must remember that it is never possible to "save a life" but only to postpone the moment of death. Further deliberations by the CAST Events Committee led to the creation of a relatively simple form that was completed by the principal investigator, the results of which agreed with the extensive Events Committee review of causes of death in 85% of cases.[22]

In reality, the most important determination is the classification of death as either cardiac or noncardiac. For example, if an antiarrhythmic drug prevents an arrhythmic death but promotes a death from congestive heart failure, that drug should not be considered effective. Not only will such a drug hasten the patient's death, but it may also erode the quality of life. The primary end point for trials of antiarrhythmic therapy probably should be total cardiac mortality, because it is simpler to assess and would provide a means to evaluate additional cardiac effects of the therapy. Nevertheless, most investigators have continued to try to assess only the antiarrhythmic effects of therapy, because a larger sample size is necessary to detect a difference between active treatment and placebo (or between 2 treatments) if total cardiac mortality is used as the primary end point. Until more accurate measures of the etiology and mechanism of cardiac death are established, until therapies become more effective and have fewer adverse effects, and until larger and longer-term studies are undertaken, it will be necessary to continue to subclassify cardiac deaths as arrhythmic and nonarrhythmic.

REFERENCES

1. Gordon T, Kannel WB. Premature mortality from coronary heart disease: the Framingham Study. *JAMA 1971;215:1617–1625.*

2. National Center for Health Statistics. Advance report, final mortality statistics, 1981. *Monthly Vital Stat Rep 1981;33:suppl DHHS:4–5.*

3. Gordon T, Thom T. The recent decrease in CHD mortality. *Prev Med 1975;4:115–125.*

4. Goldberg RJ. Declining out-of-hospital sudden coronary death rates. Additional pieces of the epidemiologic puzzle. *Circulation 1989;79:1369–1373.*

5. Gillum RF. Sudden coronary death in the United States. 1980–1985. *Circulation 1989;79:756–765.*

6. Cobb LA, Werner JA, Trobaugh GB. Sudden cardiac death: I. A decade's experience with out-of-hospital resuscitation. *Mod Concepts Cardiovasc Dis 1980;49:31–36.*

7. Weaver WD, Cobb LA, Copass MK, Hallstrom AP. Ventricular defibrillation—a comparative trial using 175-J and 320-J shocks. *N Engl J Med 1982;307:1101–1106.*

8. Cobb LA, Werner JA, Trobaugh GB. Sudden cardiac death: II. Outcome of resuscitation, management, and future directions. *Mod Concepts Cardiovasc Dis 1980;49:37–42.*

9. Baum RS, Alvarez H III, Cobb LA. Survival after resuscitation from out-of-hospital ventricular fibrillation. *Circulation 1974;50:1231–1235.*

10. Schaffer WA, Cobb LA. Recurrent ventricular fibrillation and modes of death in survivors of out-of-hospital ventricular fibrillation. *N Engl J Med 1975;293:260–262.*

11. Greene HL. The ventricular fibrillation survivor: when and how to treat. *Mod Med 1985;53:64–82.*

12. Cobb LA, Baum RS, Alvarez H III, Schaffer WA. Resuscitation from out-of-hospital ventricular fibrillation: 4 years follow-up. *Circulation 1975;51:III-223–III-228.*

13. Thompson RG, Cobb LA. Hypokalemia after resuscitation from out-of-hospital ventricular fibrillation. *JAMA 1982;248:2860–2863.*

14. Weaver WD, Cobb LA, Hallstrom AP, Copass MK, Ray R, Emery M, Fahrenbruch C. Considerations for improving survival from out-of-hospital cardiac arrest. *Ann Emerg Med 1986;15:1181–1186.*

15. Weaver WD, Hill D, Fahrenbruch GE, Copass MK, Martin JS, Cobb LA, Hallstrom AP. Use of the automatic external defibrillator in the management of out-of-hospital cardiac arrest. *N Engl J Med 1988;319:661–666.*

16. Nikolic G, Bishop RL, Singh JB. Sudden death recorded during Holter monitoring. *Circulation 1982;66:218–225.*

17. Pratt CM, Francis MJ, Luck JC, Wyndham CR, Miller RR, Quinones MA. Analysis of ambulatory electrocardiograms in 15 patients during spontaneous ventricular fibrillation with special reference to preceding arrhythmic events. *JACC 1983;2:789–797.*

18. Panidis IP, Morganroth J. Sudden death in hospitalized patients: cardiac rhythm disturbances detected by ambulatory electrocardiographic monitoring. *JACC 1983;2:798–805.*

19. Kay GN, Plumb VJ, Arciniegas JB. Torsade de pointes: the long-short initiating sequence and other clinical features: observations in 32 patients. *JACC 1983;2:806–817.*

20. Milner PG, Platia EV, Reid PR, Griffith LSC. Ambulatory electrocardiographic recordings at the time of fatal cardiac arrest. *Am J Cardiol 1985;56:588–592.*

21. de Luna AB, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmias on the basis of data from 157 cases. *Am Heart J 1989;117:151–159.*

22. The Cardiac Arrhythmia Suppression Trial Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med 1989;321:406–412.*

23. Cobb LA, Alvarez H III, Copass MK. A rapid response system for out-of-hospital cardiac emergencies. *Med Clin North Am 1976;60:283–290.*

24. Cobb LA, Hallstrom AL, Thompson RG, Mandel LP, Copass MK. Community cardiopulmonary resuscitation. *Annu Rev Med 1980;31:453–462.*

25. Cobb LA, Hallstrom AP. Community-based cardiopulmonary resuscitation: what have we learned? *Ann NY Acad Sci 1982;382:330–342.*

26. Cobb LA. Prehospital cardiac care: does it make a difference? *Am Heart J 1982;103:316–318.*

27. Mandel LP, Cobb LA. Initial and long-term competency of citizens trained in CPR. *Emerg Health Serv Q 1982;1:49–63.*

28. Hallstrom AP, Cobb LA, Swain M, Mensinger K. Predictors of hospital mortality after out-of-hospital cardiopulmonary resuscitation. *Crit Care Med 1985;13:927–929.*

29. Eisenberg MS, Copass MK, Hallstrom AP, Blake B, Bergner L, Short FA, Cobb LA. Treatment of out-of-hospital cardiac arrests with rapid defibrillation by emergency medical technicians. *N Engl J Med 1980;302:1379–1383.*

30. Thompson RG, Hallstrom AP, Cobb LA. Bystander-initiated cardiopulmonary resuscitation in the management of ventricular fibrillation. *Ann Intern Med 1979;90:737–740.*
31. Weaver WD, Copass MK, Bufi D, Ray R, Hallstrom AP, Cobb LA. Improved neurologic recovery and survival after early defibrillation. *Circulation 1984;69:943–954.*
32. Hallstrom AP, Cobb LA. Predicting risk of recurrence in sudden cardiac death syndrome. *Emerg Health Serv Rev 1984;2:49–62.*
33. Ritchie JL, Hallstrom AP, Trobaugh GB, Caldwell JH, Cobb LA. Out-of-hospital sudden coronary death: rest and exercise radionuclide left ventricular function in survivors. *Am J Cardiol 1985;55:645–651.*
34. Weaver WD, Lorch GS, Alvarez H III, Cobb LA. Angiographic findings and prognostic indicators in patients resuscitated from sudden cardiac death. *Circulation 1976;54:895–900.*
35. Weaver WD, Cobb LA, Hallstrom AP. Ambulatory arrhythmias in resuscitated victims of cardiac arrest. *Circulation 1982;66:212–218.*
36. Eisenberg MS, Hallstrom A, Berner L. Long-term survival after out-of-hospital cardiac arrest. *N Engl J Med 1982;306:1340–1343.*
37. Weaver WD, Cobb LA, Hallstrom AP. Characteristics of survivors of exertion- and nonexertion-related cardiac arrest: value of subsequent exercise testing. *Am J Cardiol 1982;50:671–676.*
38. Wilbur DJ, Garan H, Finkelstein D, Kelly E, Newell J, McGovern B, Ruskin JN. Out-of-hospital cardiac arrest. Use of electrophysiologic testing in the prediction of long-term outcome. *N Engl J Med 1988;318:19–24.*
39. Swerdlow CD, Freedman RA, Peterson J, Clay D. Determinants of prognosis in ventricular tachyarrhythmia patients without induced sustained arrhythmias. *Am Heart J 1986;111:433–438.*
40. Roy D, Waxman HL, Kienzle MC, Buxton AE, Marchlinski FE, Josephson ME. Clinical characteristics and long-term follow-up in 119 survivors of out-of-hospital cardiac arrest: relation to inducibility at electrophysiologic testing. *Am J Cardiol 1983;52:969–974.*
41. Freedman RA, Swerdlow CD, Soderholm-Difatte V, Mason JW. Prognostic significance of arrhythmia inducibility or noninducibility at initial electrophysiologic study in survivors of cardiac arrest. *Am J Cardiol 1988;61:578–582.*
42. Zheutlin TA, Steinman RT, Mattioni TA, Kehoe RF. Long-term arrhythmic outcome in survivors of ventricular fibrillation with absence of inducible ventricular tachycardia. *Am J Cardiol 1988;62:1213–1217.*
43. Morady F, DiCarlo L, Winston S, Davis JL, Scheinman MM. Clinical features and prognosis of patients with out-of-hospital cardiac arrest and a normal electrophysiologic study. *JACC 1984;4:39–44.*
44. Hallstrom AP, Cobb LA, Ray R. Smoking as a risk factor for recurrence of sudden cardiac death. *N Engl J Med 1986;314:271–275.*
45. Haynes RE, Hallstrom AP, Cobb LA. Repolarization abnormalities in survivors of out-of-hospital ventricular fibrillation. *Circulation 1978;57:654–658.*
46. Cobb LA, Weaver WD. Exercise: a risk for sudden death in patients with coronary heart disease. *JACC 1986;7:215–219.*
47. Adhar GC, Larson LW, Bardy GH, Greene HL. Sustained ventricular arrhythmias: differences between survivors of cardiac arrest and patients with recurrent sustained ventricular tachycardia. *JACC 1988;12:159–165.*
48. Swerdlow CD, Bardy GH, McAnulty J, Lee JT, Graham EL, Petersen J, Greene HL. Determinants of induced sustained arrhythmias in survivors of out-of-hospital ventricular fibrillation. *Circulation 1987;76:1053–1060.*
49. Poole JE, Marks ML, Powell JL, Maynard C, Kruse AP, Bardy GH, Ivey TD, Greene HL. Differences in surgical outcome for ventricular tachycardia and fibrillation (abstr). *JACC 1989;13:214A.*
50. The Aspirin Myocardial Infarction Study Research Group. The Aspirin Myocardial Infarction Study: final results. *Circulation 1980;62:V:V-79–V-84.*
51. Byington RP, the Beta-Blocker Heart Attack Trial Research Group. Beta-Blocker Heart Attack Trial: design, methods and baseline results. *Controlled Clin Trials 1984;5:382–437.*
52. MILIS Study Group. Multicenter Investigation of the Limitation of Infarct Size: design and methods of the clinical trial. *Am Heart Assoc Monograph No. 100:1984.*
53. Hinkle LE Jr, Thaler HT. Clinical classification of cardiac deaths. *Circulation 1982;65:457–464.*
54. Goldstein S, Friedman L, Hutchinson R, Canner P, Romhilt D, Schlant R, Sobrino R, Verter J, Wasserman A, and the Aspirin Myocardial Infarction Study Research Group. Timing, mechanism and clinical setting of witnessed deaths in postmyocardial infarction patients. *JACC 1984;3:1111–1117.*
55. Block G, Wickland B. "Sudden death"—What are we talking about? *Circulation 1972;45:256–258.*
56. Friedman M, Manwaring JH, Rosenman RH, Donlon G, Ortega P, Grube SM. Instantaneous and sudden deaths. Clinical and pathological differentiation in coronary artery disease. *JAMA 1973;225:1319–1328.*
57. WHO Scientific Group. The pathological diagnosis of acute ischemic heart disease. *WHO Techn Rep Ser 1970;441:5–27.*
58. Goldstein S. The necessity of a uniform definition of sudden coronary death: witnessed death within 1 hour of the onset of acute symptoms. *Am Heart J 1982;103:156–159.*
59. Joint International Society and Federation of Cardiology/World Health Organization Task Force on Standardization of Clinical Nomenclature. Report. Nomenclature and criteria for diagnosis of ischemic heart disease. *Circulation 1979;59:607–609.*
60. Marcus FL, Cobb LA, Edwards JE, Kuller L, Moss AJ, Bigger JT Jr, Fleiss JL, Rolnitzky L, Serokman R, and the Multicenter Post Infarction Research Group. Mechanism of death and prevalence of myocardial ischemic symptoms in the terminal event after myocardial infarction. *Am J Cardiol 1988;61:8–15.*
61. Greene HL, Richardson DW, Barker AH, Roden DM, Capone RJ, Echt DS, Friedman LM, Gillespie MJ, Hallstrom AP, Verter J, and the CAPS Investigators. Classification of deaths after myocardial infarction as arrhythmic or nonarrhythmic (The Cardiac Arrhythmia Pilot Study). *Am J Cardiol 1989;63:1–6.*

Sudden Cardiac Death: A Diversity of Causes with Focus on Atherosclerotic Coronary Artery Disease

William C. Roberts, MD

There are many causes of sudden cardiac death, and the younger the patient the more diverse the cause. Among persons dying suddenly in the Western World atherosclerotic coronary artery disease is the most common. This group might best be called atherosclerotic sudden coronary death. This article summarizes a previously published necropsy study by Warnes and Roberts of 70 victims aged 22 to 81 years (mean 50) of sudden coronary death.

Of 3,484 five-mm coronary segments examined (mean 50 per patient) from the 4 major (left main, left anterior descending, left circumflex and right) coronary arteries, 950 (27%) were narrowed 76 to 100% in cross-sectional area by plaque; 1,127 (32%), 51 to 75%; 689 (20%), 26 to 50%, and 718 (21%), 0 to 25%. More extensive severe narrowing occurred in the proximal compared with the distal halves to the left anterior descending, left circumflex and right coronary arteries. Comparison between the 31 previously symptomatic victims (either angina pectoris and/or a clinical acute myocardial infarction) to the 39 victims who had previously been asymptomatic disclosed a significantly higher mean percent of severely (76 to 100% in cross-sectional area) narrowed 5-mm segments (30 vs 25% [$p < 0.0051$]) and a lower mean percent of minimally (0 to 25%) narrowed segments in the symptomatic group (15 vs 25%, $p < 0.001$). Thus, the major coronary arteries at necropsy in victims of sudden coronary death are diffusely involved by atherosclerotic plaque and in nearly one-third of the lengths of the major arteries the lumens are narrowed >75% in cross-sectional area by plaque. The average amount of severe (>75%) narrowing is similar in the age groups 31 to 40 years, 41 to 50, 51 to 60, and 61 to 70 years.

(Am J Cardiol 1990;65:13B–19B)

From the Pathology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20892.

Address for reprints: William C. Roberts, MD, Pathology Branch, Building 10, Room 2N258, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20892.

The phrase "sudden death" has been used by lay and medical persons for nearly 450 years. It has many definitions. Sudden death might be a game played to break a tie or the extra minutes of play added to a tied game, the winning team being the first team to score. In medicine, sudden death generally denotes death which is *nonviolent* or nontraumatic, which is *unexpected*, which is *witnessed* and which is *instantaneous* or occurs within a few minutes of an abrupt change in previous clinical state. In heart disease the word "cardiac" is usually placed between the words "sudden" and "death," and the phrase "sudden cardiac death" usually is applied to persons dying suddenly from atherosclerotic coronary artery disease.[1] Necropsy studies of persons dying suddenly from cardiac disease, however, disclose many causes of sudden cardiac death, and, therefore, greater specificity is required in terms to prevent confusion (Fig. 1). Of persons dying suddenly from cardiovascular disease, the cause may be *cardiac* or *noncardiac*. The cardiac causes can be subdivided into *coronary* and *noncoronary*. Of the coronary causes, atherosclerosis is, of course, by far the most common and the term *atherosclerotic sudden coronary death* may be applied to them.[2–10] In young persons particularly, several *nonatherosclerotic* coronary conditions, mainly coronary anomalies, cause sudden death.[11–13] Of the cardiac, but noncoronary, causes of sudden death, the most common are cardiomyopathy,[14,15] particularly hypertrophic cardiomyopathy,[16,17] and valvular heart disease, most often the conditions causing left ventricular outflow obstruction,[18–23] sometimes associated with prosthetic or bioprosthetic heart valves.[24] Also, there are noncardiac but vascular causes of sudden death.[25,26] Some cardiac arrhythmic causes of sudden death not necessarily associated with morphologic abnormalities, e.g., prolonged QT interval syndrome, do not appear in Figure 1.

Some examples of the many causes of sudden cardiac death:

1. M.M., a 13-year-old athletic boy, the son of a former professional football player, collapsed while jogging and died. He had always been asymptomatic. His brother, 1 year older, had died a year earlier also while jogging. M.M.'s electrocardiogram 6 months earlier was considered "abnormal" but his left ventricular pressure was normal and there was no obstruction to left ventricular outflow.

2. A 17-year-old girl, who ran 40 miles weekly, suddenly collapsed and died just after crossing the finish line of a 3-mile race. She had been "healthy" all her life.

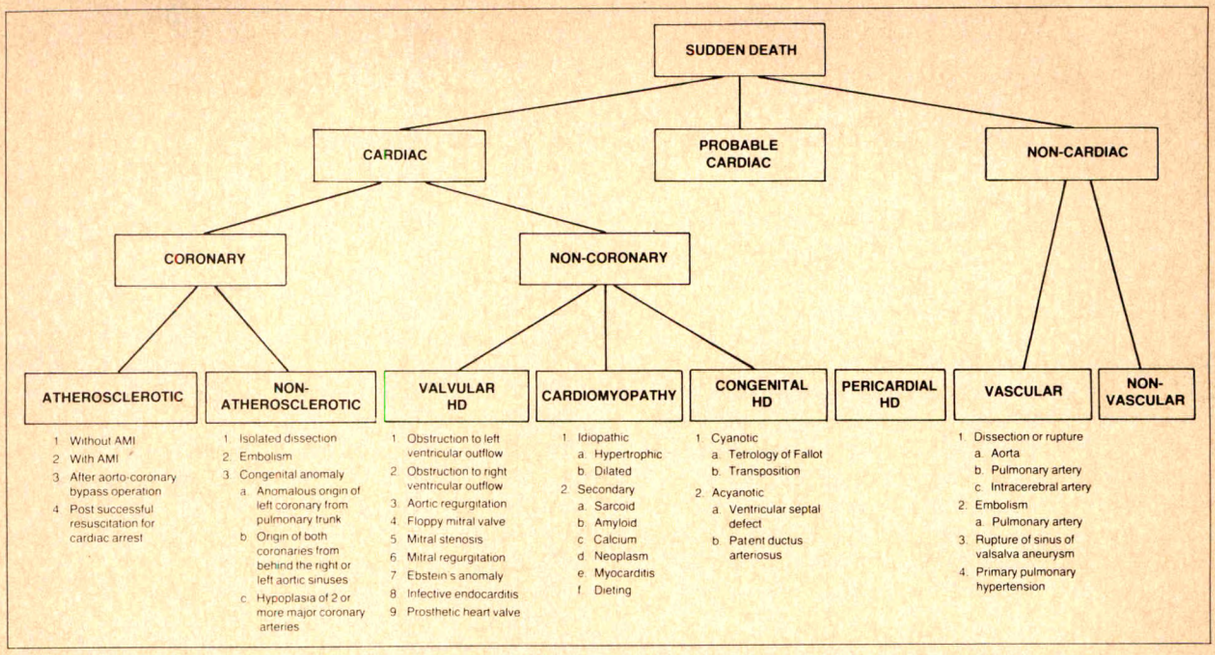


FIGURE 1. Various causes of sudden death. HD = heart disease. (Reproduced with permission from *Am J Cardiol.*[1])

3. A 19-year-old male midshipman was always asymptomatic until he suddenly collapsed and died while sitting on a bench immediately after running around the track several times. On admission examination 1 year earlier, electrocardiogram had shown ventricular premature complexes and left-axis deviation. The heart was of normal size by chest roentgenogram. The blood pressure was 135/80 mm Hg.

4. A 28-year-old woman, well all her life, suddenly collapsed and died while running for a bus.

5. A 28-year-old man died suddenly while pushing a brick-loaded wheelbarrow. He had been well until 2 days earlier when he complained of "pain in his neck," but this did not prevent him from performing his usual construction job activities.

6. A 33-year-old woman, a domestic, collapsed while at work and died immediately. She had been healthy all her life.

7. A 44-year-old woman, a secretary, collapsed while walking in her office and died. She had been asymptomatic all her life but on routine examination several years earlier was found to have precordial murmurs (each grade 2/6) consistent with "aortic stenosis and regurgitation." Chest radiograph had shown mild cardiomegaly and electrocardiogram had shown left ventricular hypertrophy.

8. A 44-year-old male taxicab driver was well until 1 hour before death when he became enraged because his taxicab was bombarded by snowballs thrown by 3 youths. One snowball entered an open window and hit him in the face, knocking off his glasses. He immediately radioed the police who arrived several minutes later and apprehended the youths. The police described the taxicab driver as "livid with rage" over the incident and advised him to leave the scene. Thirty minutes later he radioed his dispatcher that he was having breathing difficulties. He arrived at the dispatcher's office a few minutes later, collapsed and died.

9. A 60-year-old male school teacher had been well all his life except for recognized systemic hypertension until a few minutes before death when he became enraged when trying to prevent 2 students in the school gymnasium from fighting. He finally broke up the fight and, while walking away from the event minutes later, collapsed and died.

10. An 81-year-old woman, who had had a pacemaker inserted for complete heart block 23 months earlier, collapsed and died while climbing a flight of stairs in her home. During the preceeding 2 days, she had noted excessive fatigue, nausea and vomiting.

The cause of death in each of these 10 patients was different and had not a necropsy been performed the cause of death could not have been accurately predicted. Patient 1 had *hypertrophic cardiomyopathy*. Patient 2 had *congenital hypoplasia of both right and left circumflex coronary arteries with inadequate perfusion of the posterior wall of the left ventricle*.[27] Patient 3 had *origin of the left main coronary artery from the right sinus of Valsalva with coursing of the left main between the pulmonary trunk and ascending aorta*.[28] Patient 4 had *isolated coronary arterial dissection* involving the left anterior descending and left circumflex coronary arteries.[29] Patient 5 had extensive *cardiac sarcoidosis*.[15] Patient 6 had a *ruptured sinus of Valsalva aneurysm* (into the pericardial sac rather than into the right side of the heart).[30] Patient 7 had *congenital origin of the left main coronary artery from the pulmonary trunk*.[12] Patient 8 had *atherosclerotic coronary artery disease* with severe

narrowing of each of the 3 major coronary arteries. Patient 9 had a large heart (550 g [normal ≤400 g]) from *systemic hypertension* but no significant coronary arterial narrowing or other recognized cause of sudden death.[31] Patient 10 had severe *coronary arterial atherosclerosis* with *acute myocardial infarction* complicated by *rupture of the left ventricular free wall* and hemopericardium.[32] Tests of the pacemaker after death disclosed that it had functioned normally.

In any study discussing sudden death from cardiovascular disease, the word *sudden* needs defining. The World Health Organization has used a 24-hour definition of sudden, meaning, of course, death occurring within 24 hours from an abrupt change in previous clinical status.[33] When this definition of sudden is used, many cases of acute myocardial infarction are intermixed with cases of sudden atherosclerotic coronary death unassociated with myocardial necrosis. Because it takes over 6 hours for histologic evidence of myocardial necrosis to be apparent and because most persons dying suddenly do so within an hour of change in previous clinical status, the 6-hour definition for sudden when applied to "atherosclerotic sudden coronary death" more clearly separates the infarct cases from the noninfarct ones.

Although the term sudden implies *unexpected*, in only one-quarter of victims of atherosclerotic coronary artery disease is sudden death the initial manifestation of coronary artery disease, and therefore, truly unexpected. Sudden death in patients with angina pectoris or healed myocardial infarction is really not so unexpected. Likewise, in persons with hypertrophic cardiomyopathy and certain forms of valvular heart disease, death suddenly is always a shock but, in actuality, not so unexpected.

Although sudden death is usually reserved for *nonviolent* or nontraumatic deaths, various mentally or even physically traumatic events can precipitate sudden death.[34–36]

The term "sudden death" is often used for persons in hospitals who are found dead, most often in their beds. I try to reserve the term "sudden death" for persons who have fatal or nonfatal cardiac arrest *outside* the hospital or at least whose symptoms of cardiovascular dysfunction appear initially while outside a hospital. Some of these victims, of course, are rushed to hospitals where fatal cardiac arrest occurs shortly after arrival.

I have examined many manuscripts which have used the phrase "sudden death" as a *cause* of death: "Patient so and so died of sudden death or patient so and so had sudden death but lived!" Obviously, the term "sudden death" should be used only as a *mode* of death or otherwise lawyers and editors will have a field day.

The use of the term "sudden death" in persons who are successfully resuscitated is not recommended. The use of the term *nonfatal cardiac arrest* (to contrast with *fatal cardiac arrest*) is preferable in this circumstance.

Thus, sudden cardiac death has many causes. Atherosclerotic coronary artery disease, obviously, is by far the most common cause of sudden cardiac death, but the latter term is not synonomous with atherosclerotic coronary artery disease. The term "sudden coronary death" is not ideal either because not all sudden coronary deaths are the result of atherosclerotic narrowing, but "sudden coronary death" is more precise than "sudden cardiac death." Sudden death is not always so *sudden*, or so *unexpected* or *witnessed*, and indeed it may be caused by or precipitated by mental or physical violence. Thus, greater precision is needed when discussing sudden cardiac death.

ATHEROSCLEROTIC CORONARY ARTERY DISEASE

Warnes and I[8] studied at necropsy 70 victims of sudden coronary death to determine the amount and distribution of cross-sectional area luminal narrowing in each 5-mm segment of the 4 major coronary arteries, and compared the amount of narrowing both qualitatively and quantitatively in those with and without previous clinical evidence of myocardial ischemia.

All patients fulfilled the following criteria: (1) Death was known to occur within 6 hours of the previously witnessed usual state of health. (2) Although the patient may have died in a hospital, he/she was not a patient in a hospital at the onset of symptoms suggestive of myocardial ischemia. (3) At necropsy, ≥1 of the 4 major (left main, left anterior descending, left circumflex and right) coronary arteries was narrowed 76 to 100% cross-sectional area. (4) Ventricular myocardial coagulation necrosis was absent (histologic examination) at necropsy. (5) A cause of death, cardiac or noncardiac, other than coronary artery disease was absent. (6) Chronic congestive heart failure had never been present. (7) A cardiovascular operation had never been performed. Review of clinical and necropsy records in the Pathology Branch, National Heart, Lung, and Blood Institute, yielded 63 men and 7 women aged 22 to 81 years (mean 50) fulfilling these criteria. Of the 70 victims, 46 died outside the hospital. The other 24 had chest pain outside the hospital and had fatal cardiac arrest shortly after being brought to the hospital.

The hearts were fixed for ≥24 hours in formalin. The 4 major coronary arteries were excised intact, x-rayed and decalcified if necessary. Each artery was then cut transversely into 5-mm segments and labeled sequentially, either from the aortic ostium, or from its origin from the left main coronary artery. The segments were then dehydrated with alcohol and xylene, embedded in paraffin, and at least 2 histologic sections were cut from the paraffin block. Each histologic section was stained by the Movat technique. The amount of luminal narrowing by atherosclerotic plaque was determined by visual inspection of these histologic sections when magnified 25 to 50 times. The percent of cross-sectional area narrowing of each 5-mm segment was categorized into 5 groups: 0 to 25, 26 to 50, 51 to 75, 76 to 95 and 96 to 100. All sections were examined and the accuracy of the assessment of luminal narrowing was spot-checked by video planimetry. A total of 3,484 five-mm segments from the 70 victims were examined (mean number of segments per patient = 50).

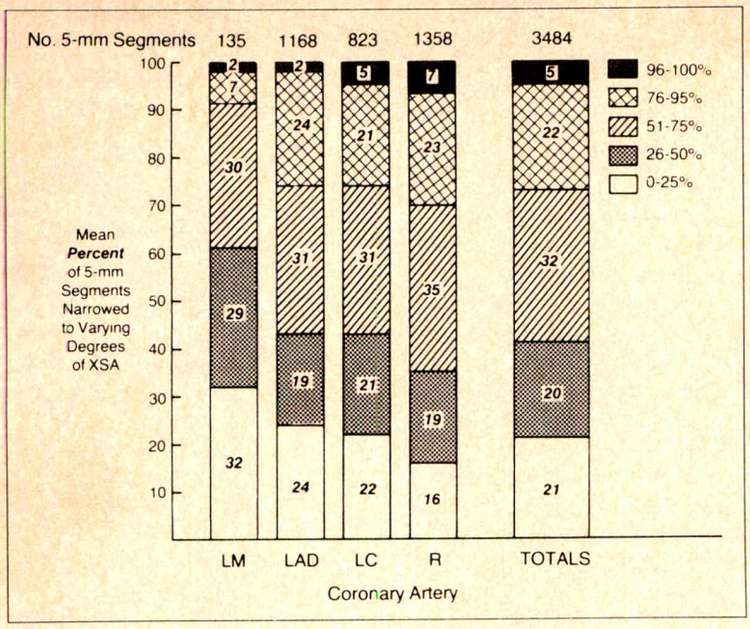


FIGURE 2. Mean percents of 5-mm segments of the 4 major coronary arteries narrowed to varying degrees in cross-sectional area (XSA) in 70 patients with sudden coronary death. LAD = left anterior descending; LC = left circumflex; LM = left main; R = right. (Reproduced with permission from *Am J Cardiol.*[5])

Qualitative studies: Of the 70 patients, 1 major coronary artery was narrowed 76 to 100% in cross-sectional area *at some point* in 11 patients (16%), 2 arteries in 19 (27%), 3 arteries in 33 (47%), and 4 arteries in 7 (10%). Of the 280 major epicardial coronary arteries in the 70 patients (4 per patient), 176 (63%) were narrowed at some point 76 to 100% in cross-sectional area, a mean of 2.5 of 4.0 major coronary arteries per patient. Excluding the left main coronary artery, 167 (80%) of the other 210 major coronary arteries were narrowed 76 to 100% in cross-sectional area, an average of 2.4 of 3.0 coronary arteries per patient. Of the individual major coronary arteries, the left main was severely (76 to 100% in cross-sectional area) narrowed in 13% (9 of 70), the left anterior descending in 86% (60 of 70), the left circumflex in 74% (52 of 70), and the right in 79% (55 of 70).

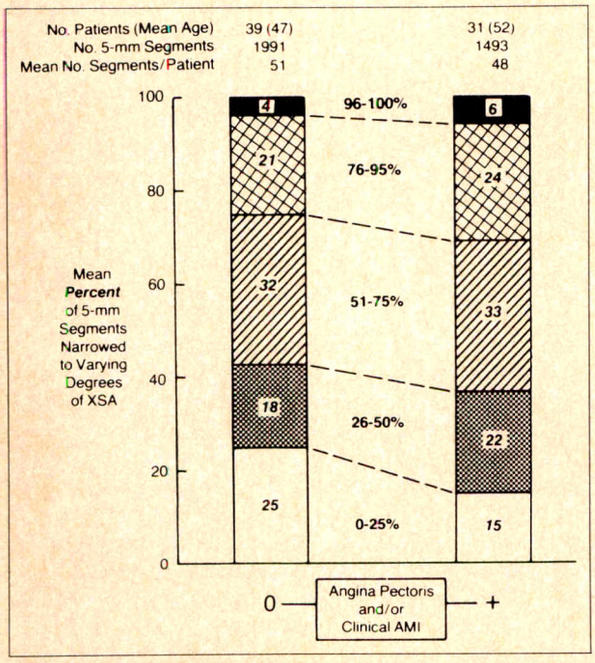


FIGURE 3. Mean percents of 5-mm segments of the sum of the 4 major coronary arteries narrowed to varying degrees in cross-sectional area (XSA) in 70 patients with sudden coronary death: comparison of 39 patients without and 31 patients with a clinical acute myocardial infarction (AMI) and/or angina. (Reproduced with permission from *Am J Cardiol.*[5])

Comparison of the number of coronary arteries narrowed 76 to 100% in cross-sectional area in the 39 previously *asymptomatic* patients to the 31 with *previous acute myocardial infarction and/or angina pectoris* disclosed the following: 1 major artery so narrowed in 8 (21%) vs 3 (10%) (difference not significant [NS]); 2 arteries, 11 (28%) vs 8 (26%) (NS); 3 arteries, 18 (46%) vs 15 (48%) (NS), and 4 arteries, 2 (5%) vs 5 (16%) (NS).

Comparison of the number of arteries narrowed 76 to 100% in cross-sectional area in the 39 patients without to the 31 with a *healed myocardial infarct* revealed the following: 1 major artery so narrowed in 9 (23%) vs 2 (7%) (NS); 2 arteries, 11 (28%) vs 8 (26%) (NS); 3 arteries, 13 (33%) vs 20 (64%) ($p < 0.02$), and 4 arteries, 6 (15%) vs 1 (3%) (NS).

Quantitative studies: Analysis of the 3,484 five-mm coronary segments showed that 950 (27%) were narrowed 76 to 100% in cross-sectional area; 1,127 (32%), 51 to 75%; 689 (20%), 26 to 50%, and 718 (21%), 0 to 25% (Fig. 2). The percent of segments severely narrowed per patient, however, varied enormously; from 2% (1 of 50) to 88% (86 of 98). Sixteen patients had ≤10% of their 5-mm segments narrowed 76 to 100% in cross-sectional area; 15 patients had 11 to 20% of the segments so narrowed; 11 patients, 21 to 30% of the segments; 16 patients, 31 to 40% of the segments; 7 patients, 41 to 50% of the segments; 2 patients, 51 to 60% of the segments; 2 patients,

61 to 70% of the segments, and 1 patient had 81 to 90% of the segments so narrowed. Comparison of the mean percent of 5-mm segments narrowed 76 to 100% in cross-sectional area in the arteries' proximal and distal halves disclosed a significantly higher percent of severely narrowed segments proximally in the left anterior descending and left circumflex coronary arteries than in the distal portion of these arteries, but a similar percent in the proximal and distal halves of the right coronary artery.

Of the 39 patients who had been asymptomatic, 502 (25%) of 1,991 five-mm segments were narrowed 76 to 100% in cross-sectional area compared with 448 (30%) of 1,493 five-mm segments in the 31 patients who had had either a clinical acute myocardial infarction and/or angina pectoris previously ($p < 0.005$) (Fig. 3). Comparison of the mean percents of segments in all 5 categories of cross-sectional area coronary narrowing between the previously *asymptomatic* and *symptomatic* groups disclosed significant differences in the category of minimal (0 to 25%) cross-sectional area narrowing (25 vs 15%, $p < 0.001$). Comparison of the amounts of narrowing in each of the 4 major coronary arteries disclosed a higher mean percent of 5-mm segments narrowed 76 to 100% in cross-sectional area in the symptomatic vs the asymptomatic victims in the left main, left anterior descending and left circumflex, but not in the right coronary arteries, and a lower mean percent of segments narrowed 0 to 25% in cross-sectional area in all 4 coronary arteries in the symptomatic group.

Comparison of the mean percents of 5-mm segments in the 5 categories of narrowing between the 31 patients with and the 39 patients without *left ventricular scars* disclosed a higher mean percent of segments narrowed 76 to 100% in the healed myocardial infarction group (33 vs 24%, $p < 0.001$), and lower mean percent of segments narrowed 0 to 25% (13 vs 26%, $p < 0.001$) compared to those without healed myocardial infarction (Fig. 4). A higher mean percent of 5-mm segments were minimally narrowed in those with no healed myocardial infarction, and a higher mean percent of segments were severely narrowed when a healed myocardial infarction was present. Severe narrowing of the left main coronary artery, however, occurred more frequently in those without healed myocardial infarction.

Of the 70 patients, 13 at necropsy had a thrombus in 1 coronary artery.[10] In 6 patients, the thrombus consisted primarily of fibrin and erythrocytes, and in 7 patients, nearly entirely of platelets. In all 13 patients, the thrombi were superimposed on atherosclerotic plaques which had already narrowed the lumina 26 to 50% (1 patient), 51 to 75% in cross-sectional area (4 patients) or 76 to 100% (8 patients).

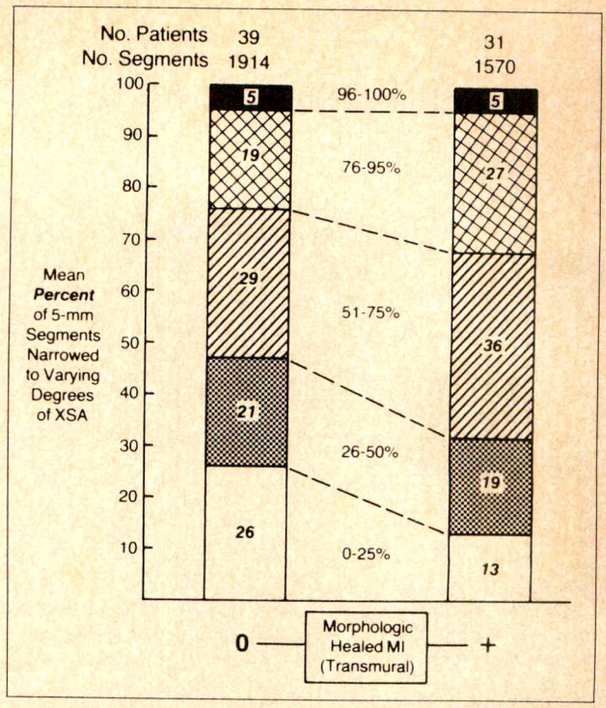


FIGURE 4. Mean percents of 5-mm segments of the sum of the 4 major coronary arteries narrowed to varying degrees in cross-sectional area (XSA) in 70 patients with sudden coronary death: comparison of 39 patients without and 31 patients with a morphologic healed myocardial infarction (MI). (Reproduced with permission from *Am J Cardiol.*[8])

DISCUSSION

A major finding in the aforementioned study was that the sudden death victims had severe and extensive narrowing of their 4 major extramural coronary arteries by atherosclerotic plaque. Of the 70 patients, 59 (84%) had ≥2 major arteries narrowed 76 to 100% in cross-sectional area and 11 (16%) had only 1 artery so narrowed by atherosclerotic plaque. Of the 59 patients with multivessel coronary artery disease, 2 arteries were severely (76 to 100% in cross-sectional area) narrowed in 19 patients (27%), 3 arteries in 33 (47%) and 4 arteries in 7 (10%). Of the 4 major coronary arteries per patient, 2.5 of 4 were severely narrowed. Of the 280 major coronary arteries in the 70 patients, 176 (63%) were narrowed severely, and of them, the left anterior descending was the most frequently narrowed artery (60 of 70 = 86%). The 11 patients with 1-vessel coronary artery disease were significantly younger than the 59 patients with multivessel coronary artery disease (mean age 41 vs 51 years).

Warnes and I[8] found the number of coronary arteries to be severely narrowed at some point (the qualitative approach) in the groups of patients with and without previous angina pectoris and/or acute myocardial infarction, and the groups with and without grossly visible left ventricular scars at necropsy to be roughly similar. Of our 70 patients, 31 (44%) had had previous clinical acute myocardial infarction (which healed) and/or angina, and 39 did not. Comparison of those with previous clinical evidence of myocardial ischemia to those without disclosed similar percents of total coronary arteries (4 per patient) severely narrowed (84 of 124 [68%] vs 92 of 156 [59%]) and roughly similar percents of ≥2 coronary arteries severely narrowed (28 of 31 [90%] vs 31 of 39 [79%]). Comparison of the 31 patients with to the 39 without left ventricular scars disclosed similar percents of

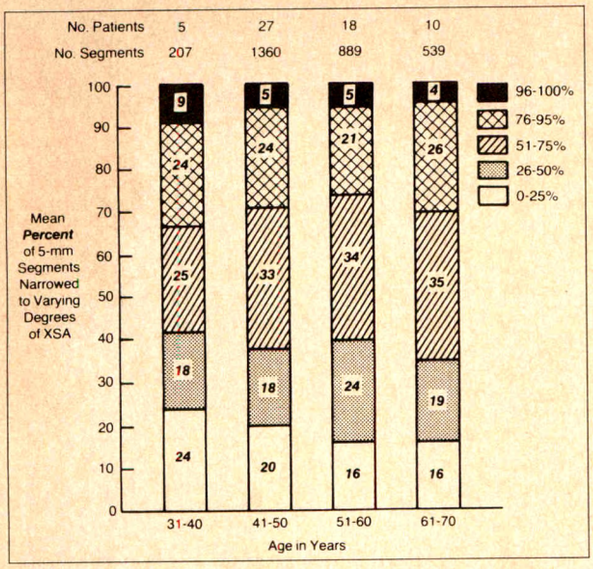


FIGURE 5. Relation of age to the mean percent of 5-mm coronary segments narrowed to varying degrees in 60 men with sudden coronary death. XSA = cross-sectional area. (Reproduced with permission from *Am Heart J.*[9])

total coronary arteries severely narrowed (82 of 124 [66%] vs 94 of 156 [60%]) and similar percents of ≥2 coronary arteries severely narrowed (29 of 31 [94%] vs 30 of 39 [77%]).

Of the 39 patients who previously had had no clinical evidence of myocardial ischemia (asymptomatic group), 25% of 5-mm segments were narrowed 76 to 100% in cross-sectional area compared with 30% in those who had had symptoms of ischemia (acute myocardial infarction which healed and/or angina pectoris) ($p < 0.05$). The asymptomatic group also had a higher mean percent of segments minimally narrowed (25 vs 15%, $p < 0.001$).

Similar differences were apparent in the quantitative comparisons between those victims who had a healed myocardial infarction at necropsy and those who did not. More 5-mm segments were narrowed 76 to 100% in those with than in those without a left ventricular scar (33 vs 24%, $p < 0.001$); fewer 5-mm segments were minimally narrowed in those with compared to those without myocardial infarction (13 vs 26%, $p < 0.001$). Although a higher percentage of the 5-mm segments from the sum of all 4 major coronary arteries were severely narrowed in the patients with compared to those without healed myocardial infarction, analysis of the individual arteries disclosed that the left main coronary artery was different from the other 3. In the 31 patients with healed myocardial infarction only 4% of the 57 five-mm segments of left main were severely narrowed; in contrast, in the 39 patients without healed myocardial infarction, 12% of the 78 five-mm segments were severely narrowed.

Although the study by Warnes and I[8] disclosed the patients as a group to have severe and extensive coronary narrowing by atherosclerotic plaque, considerable variation in the percent of 5-mm segments narrowed severely was observed. The range was from 2 to 86%: 16 patients (23%) had <10% of their coronary segments narrowed 76 to 100% in cross-sectional area and 12 patients (17%) had >40% of their 5-mm segments severely narrowed. Thus, the extent of the severe narrowing is difficult to predict in the individual patient, but predictable in groups of patients dying suddenly from coronary artery disease. The previously symptomatic patients clearly had more severe narrowing and less minimal narrowing than the asymptomatic group, as did those patients with compared to those without a healed myocardial infarction.

The average amount of coronary narrowing in patients with atherosclerotic sudden coronary death was similar in both younger and older victims.[9] Among 60 men (all included in the aforementioned study) aged 31 to 70 years with atherosclerotic sudden coronary death, Warnes and I[9] found similar mean percents of 5-mm-long coronary segments narrowed severely (>75% in cross-sectional area) in each of 4 decades: 33% in the 5 patients aged 31 to 40 years, 29% in the 27 patients aged 41 to 50 years, 26% in the 18 patients aged 51 to 60 years, and 30% in the 10 patients aged 61 to 70 years (Fig. 5). The mean percent of 5-mm segments minimally narrowed (0 to 25%), however, was significantly higher in the younger than in the older decades. Thus, as groups, both young and old victims of sudden coronary death have similar amounts of severe coronary narrowing, but the younger victims have a greater proportion of their major coronary arteries minimally narrowed.

REFERENCES

1. Roberts WC. Sudden cardiac death: definitions and causes. *Am J Cardiol 1986;57:1410–1413.*

2. Roberts WC, Buja LM. The frequency and significance of coronary arterial thrombi and other observations in fatal acute myocardial infarction. A study of 107 necropsy patients. *Am J Med 1972;52:426–443.*

3. Roberts WC, Jones AA. Quantitation of coronary arterial narrowing at necropsy in sudden coronary death. Analysis of 31 patients and comparison with 25 control subjects. *Am J Cardiol 1979;44:39–45.*

4. Waller BF, Roberts WC. Sudden death while running in conditioned runners aged 40 or over. *Am J Cardiol 1980;45:1292–1300.*

5. McManus BM, Waller BF, Graboys TB, Mitchell JH, Siegel RJ, Miller HS Jr, Froelicher VF, Roberts WC. Exercise and sudden death. Part I. *Curr Probl Cardiol 1982;6(9):1–89.*

6. McManus BM, Waller BF, Graboys TB, Mitchell JH, Siegel RJ, Miller HS Jr, Froelicher BF, Roberts WC. Exercise and sudden death. Part II. *Curr Probl Cardiol 1982;6(10):1–57.*

7. Roberts WC, Curry RC Jr, Isner JM, Waller BF, McManus BM, Mariani-Constantini R, Ross AM. Sudden death in Prinzmetal's angina with coronary spasm documented by angiography. Analysis of three necropsy patients. *Am J Cardiol 1982;50:203–210.*

8. Warnes CA, Roberts WC. Sudden coronary death: relation of amount and distribution of coronary narrowing at necropsy to previous symptoms of myocardial ischemia, left ventricular scarring and heart weight. *Am J Cardiol 1984;54:65–73.*

9. Warnes CA, Roberts WC. Comparison at necropsy by age group of amount and distribution of narrowing by atherosclerotic plaque in 2995 five-mm long segments of 240 major coronary arteries in 60 men aged 31 to 70 years with sudden coronary death. *Am Heart J 1984;108:431–435.*

10. Warnes CA, Roberts WC. Sudden coronary death: comparison of patients with to those without coronary thrombus at necropsy. *Am J Cardiol 1984;54: 1206–1211.*

11. Roberts WC, Robinowitz M. Anomalous origin of the left anterior descending coronary artery from the pulmonary trunk with origin of the right and left circumflex coronary arteries from the aorta. *Am J Cardiol 1984;54:1381–1383.*

12. Roberts WC. Major anomalies of coronary arterial origin seen in adulthood. *Am Heart J 1986;111:941–963.*

13. Kragel AH, Roberts WC. Anomalous origin of either the right or left main coronary artery from the aorta with subsequent coursing between aorta and pulmonary trunk: analysis of 32 necropsy cases. *Am J Cardiol 1988;62:771–777.*

14. Roberts WC, Siegel JM, McManus BM. Idiopathic dilated cardiomyopathy: analysis of 152 necropsy patients. *Am J Cardiol 1987;60:1340–1355.*

15. Roberts WC, McAllister HA Jr, Ferrans VJ. Sarcoidosis of the heart. A clinicopathologic study of 35 necropsy patients (Group I) and review of 78 previously described necropsy patients (Group II). *Am J Med 1977;63:86–108.*
16. Maron BJ, Roberts WC, Epstein SE. Sudden death in hypertrophic cardiomyopathy: a profile of 78 patients. *Circulation 1982;65:1388–1394.*
17. Roberts CS, Roberts WC. Morphologic features of hypertrophic cardiomyopathy. In: Zipes DP, Rowlans DJ, eds. Progress in Cardiology. *Philadelphia: Lea & Febiger, 1989:(2/2):3–32.*
18. Morrow AG, Fort L III, Roberts WC, Braunwald E. Discrete subaortic stenosis complicated by aortic valvular regurgitation. Clinical, hemodynamic, and pathologic studies and the results of operative treatment. *Circulation 1965; 31:163–171.*
19. Roberts WC. The structure of the aortic valve in clinically-isolated aortic stenosis. An autopys study of 162 patients over 15 years of age. *Circulation 1970;42:91–97.*
20. Roberts WC. The congenitally bicuspid aortic valve. A study of 85 autopsy cases. *Am J Cardiol 1970;26:72–83.*
21. Roberts WC. Anatomically isolated aortic valvular disease. The case against its being of rheumatic etiology. *Am J Med 1970;49:151–159.*
22. Roberts WC, Perloff JK, Costantino T. Severe valvular aortic stenosis in patients over 65 years of age. A clinicopathologic study. *Am J Cardiol 1971;27:497–506.*
23. Falcone MW, Roberts WC, Morrow AG, Perloff JK. Congenital aortic stenosis resulting from unicommissural valve. Clinical and anatomic features in twenty-one adult patients. *Circulation 1971;44:272–280.*
24. Roberts WC. The silver anniversary of cardiac valve replacement. *Am J Cardiol 1985;56:503–506.*
25. Roberts WC. The aorta: its acquired diseases and their consequences as viewed from a morphologic perspective. In: Lindsay J Jr, Hurst JW, eds. The Aorta. *New York: Grune & Stratton, 1979:51–117.*
26. Roberts WC. Aortic dissection: anatomy, consequences, and causes. *Am Heart J 1981;101:195–214.*
27. Maron BJ, Roberts WC, McAllister HA, Rosing DR, Epstein SE. Sudden death in young athletes. *Circulation 1980;62:218–229.*
28. Barth WC III, Roberts WC. Left main coronary artery originating from the right sinus of Valsalva and coursing between the aorta and pulmonary trunk. *JACC 1986;7:366–373.*
29. Bulkley BH, Roberts WC. Dissecting aneurysm (hematoma) limited to coronary artery. A clinicopathologic study of six patients. *Am J Med 1973; 55:747–756.*
30. Roberts WC. Congenital cardiovascular abnormalities usually silent until adulthood. In: Roberts WC, ed. Adult Congenital Heart Disease. *Philadelphia: FA Davis, 1987:631–691.*
31. Kragel AH, Roberts WC. Sudden death and cardiomegaly unassociated with coronary, valvular, congenital or specific myocardial disease. *Am J Cardiol 1988;61:659–660.*
32. Mann JM, Roberts WC. Rupture of the left ventricular free wall during acute myocardial infarction: analysis of 138 necropsy patients and comparison with 50 necropsy patients with acute myocardial infarction without rupture. *Am J Cardiol 1988;62:847–859.*
33. Classification of atherosclerotic lesions. Report of a study group. *WHO Techn Rep Ser 1958 (No. 143).*
34. Engel GL. Sudden and rapid death during psychological stress. Forklore or folk wisdom? *Ann Intern Med 1971;74:771–782.*
35. Engel GL. Psychologic stress, vasodepressor [vasovagal] syncope, and sudden death. *Ann Intern Med 1978;89:403–412.*
36. Roberts WC. The most powerful cause of sudden death. *Am J Cardiol 1986;57:190.*

The Cardiac Arrhythmia Suppression Trial: Background, Interim Results and Implications

Craig M. Pratt, MD, and Lemuel A. Moye, MD, PhD

The Cardiac Arrhythmia Suppression Trial (CAST) was designed to test the hypothesis that suppression of ventricular premature complexes (VPCs) in survivors of acute myocardial infarction would reduce arrhythmic death risk. Instead, a preliminary finding from the CAST was that the encainide and flecainide groups had a 3.6-fold increase in arrhythmic death compared with their placebo group. These unfortunate results were especially surprising in that the CAST population represented patients in whom the risk of arrhythmic death was only moderate and the risk of proarrhythmia was thought to be low. In contrast, the arrhythmic death rate of the CAST placebo group was unusually low, to the extent that it paralleled the arrhythmic death rate in previous clinical trials of patients surviving myocardial infarction with no ventricular arrhythmia. The excessive arrhythmic death rate in patients taking encainide and flecainide occurred over the duration of the CAST, implying a proarrhythmic effect that may be due to mechanisms that are unique in this population, and thus challenging traditional concepts of proarrhythmia.

The existing knowledge regarding the proarrhythmic and negative inotropic effects of encainide and flecainide are reviewed. The previous pharmaceutical database experience with these 2 antiarrhythmic drugs exceeded 3,000 patients; however, there was no indication of this serious proarrhythmic effect. In contrast, the CAST population taking encainide and flecainide totaled only 725 patients who were followed for 10 months and had an extremely high proarrhythmic event rate. The reasons for this discrepancy are discussed. The results of the CAST emphasize the power of a randomized, placebo-controlled clinical trial to uncover previously unsuspected benefits or liabilities of traditional therapies.

(Am J Cardiol 1990;65:20B–29B)

From the Section of Cardiology, Department of Internal Medicine, Baylor College of Medicine and the School of Public Health, University of Texas Health Science Center, Houston, Texas.

Address for reprints: Craig M. Pratt, MD, Director, Clinical Cardiology Research, Baylor College of Medicine, Director, Coronary Care Unit, The Methodist Hospital, 6535 Fannin, MS F1001, Houston, Texas 77030

The Cardiac Arrhythmia Suppression Trial (CAST) was instituted in 1986 by the National Heart, Lung, and Blood Institute (NHLBI) after the completion of a 502-patient pilot study, the Cardiac Arrhythmia Pilot Study (CAPS). During a routine interim analysis of the CAST, the Data and Safety Monitoring Board discovered an unsuspected increase in arrhythmic deaths in the encainide/flecainide group compared with placebo (relative risk = 3.6).[1] As a result, patients randomized to the encainide/flecainide treatment sections of the CAST have been reevaluated and reassigned to alternative therapies. Although surprising and unfortunate, these findings represent a milestone in sudden cardiac death research and have major implications for clinical practice, our concepts regarding "proarrhythmia," and the future of antiarrhythmic drug development. This study begins with a review of knowledge regarding the risk associated with spontaneous ventricular arrhythmias at the time of planning the CAPS, followed by a discussion of the results and limitations of the CAPS. With this background the CAST study design, the interim results and their implications are discussed.

STATE-OF-THE-ART BEFORE CAPS

A number of studies have demonstrated a relation between the presence of ventricular premature complexes (VPCs) in patients surviving acute myocardial infarction (MI) and arrhythmic death.[2–6] The most comprehensive of these trials has shown an independent association between the presence of ventricular arrhythmia (VPCs ≥3/hour or ≥1 runs or nonsustained ventricular tachycardia [VT], or both) and an increased rate of arrhythmic death over 2 years.[2] Whereas the status of left ventricular function is the most powerful predictor of long-term outcome after acute MI, the studies by Bigger et al[2] and Ruberman et al[3] (combined observations of >2,500 patients) are consistent, and support the concept that VPCs are an independent risk factor for arrhythmic death. Although detection of VPCs on Holter recordings is associated with an increased arrhythmic death mortality, this marker is far from being a perfect screening test for predicting sudden death potential in survivors of acute MI. Table I depicts the sensitivity and specificity of various VPC rates in 3 published trials. Holter criteria in the range of 3 to 10 VPCs/hour identify about 50% of the patients who will die a presumed arrhythmic death over the next 1 to 2 years.[2,3,7]

Trials of the empiric administration of β blockers to patients surviving acute MI have demonstrated that such therapy (propranolol, timolol, metoprolol, atenolol) re-

TABLE I Sensitivity and Specificity of Holter Criteria for Arrhythmic Death

Trial	Holter Criteria* (VPCs)	Sample Size with VPC Criterion	True Positive†	False Positive	True Negative	False Negative†	Sens.	Spec.
Bigger et al[2]	≥3	245/819	31/245	214/245	543/574	31/574	0.50	0.72
Ruberman et al[3]	≥10	454/1,739	69/454	385/454	1,227/1,285	58/1,285	0.54	0.76
BHAT[7]	Any	1,380/1,640	70/1,380	1,310/1,380	254/260	6/260	0.92	0.16
Placebo group	≥10	211/1,640	19/211	192/211	1,372/1,429	57/1,429	0.25	0.88

* VPC rates expressed as per hour.
† Refers to arrhythmic deaths.
BHAT = Beta Blocker Heart Attack Trial; Sens. = sensitivity; Spec. = specificity; VPC = ventricular premature complexes.

duces arrhythmic death mortality after acute MI.[8–12] In contrast, all studies of empiric therapy with antiarrhythmic drugs given to patients surviving acute MI have failed to show any mortality benefit.[13] Thus, at the time of the planning of the CAPS, there had been no trial of sufficient size to address the hypothesis that suppression of ventricular arrhythmias in survivors of acute MI could reduce sudden death mortality.

Due to the limited data regarding the safety and efficacy of antiarrhythmic drugs in patients surviving acute MI, the CAPS was designed,[14] the results of which have been published.[15] The most important issues that the CAPS addressed were (1) the timing and methods of screening for ventricular arrhythmias in survivors of acute MI; (2) the degree to which the VPCs could be suppressed by antiarrhythmic drugs; (3) the ability to test multiple doses of antiarrhythmic drugs using a parallel double-blind placebo-controlled design; (4) the degree to which VPC suppression could be maintained for 1 year; and (5) the incidence of proarrhythmic effects, detrimental effects on left ventricular dysfunction, and other drug toxicities (safety issues).

CAPS

Some of the key design features of the CAPS trial are presented in Table II. For comparative purposes later in this article, the design features of the CAST are also presented. A detailed discussion of the considerations that led to the final study design and drug selection in the CAPS is available.[14]

Results of the CAPS: The primary efficacy goal of the CAPS was the frequency with which antiarrhythmic drugs could suppress at least 70% of VPCs and 90% of the runs of nonsustained VT in patients 6 to 60 days after acute MI.[14] Lower efficacy criteria were considered but rejected because they would too often be confused with VPC variability.[16,17] It was hoped that antiarrhythmic drugs could be identified that could achieve the ≥70% VPC suppression goal in ≥75% of patients tested. The pilot study allowed evaluation of multiple antiarrhythmic drugs at various doses, thus identifying antiarrhythmic drugs that achieved the CAPS efficacy goal. The VPC suppression goal was achieved in 79 and 83% of patients, respectively, using encainide and flecainide. Moricizine achieved this goal in 66% of patients, imipramine in 52%,

TABLE II Comparison of Selected Design Features of CAPS and CAST

Design Features	CAPS	CAST
Parallel placebo group	+	+
Double blind	+	+
VPC/hr	≥10	≥6
LVEF limits	LVEF ≥20%	LVEF ≤55% (6–90 days), LVEF ≤40% (91 days–2 yrs)
Time from MI	6–60 days	6–90 days (LVEF <55%), 91 days–2 yrs (LVEF <40%)
Age cutoff (yr)	<75	<80
Open-label drug titration	0	+
Antiarrhythmic drugs	Encainide, flecainide, moricizine, imipramine, placebo	Encainide, flecainide*, moricizine, placebo
Beta-blocker therapy	Encouraged	Encouraged
VPC suppression goal†	70% VPC reduction	80% VPC reduction
VT suppression goal†	90% VT reduction if ≥10 runs 100% VT reduction if ≤10 runs	90% VT reduction if ≥5 runs 100% VT reduction if ≤5 runs
Definition of nonsustained VT	3–9 consec. VPC ≥100/min	3–15 consec. VPC ≥120/min
VT proarrhythmia definition	>50 runs/day if <5 runs, >10 × increase if ≥5 runs, new VT, length ≥10 consecutive VPCs	>50 runs/day if <5 runs, >10 × increase if ≥5 runs, new VT, length ≥15 consecutive VPCs

* Flecainide considered only for patients with LVEF >30%.
† Holter on antiarrhythmic drug compared with baseline Holter.
CAPS = Cardiac Arrhythmia Pilot Study; CAST = Cardiac Arrhythmia Suppression Trial; consec. = consecutive; LVEF = left ventricular ejection fraction; MI = myocardial infarction; VPC = ventricular premature complexes; VT = ventricular tachycardia.

TABLE III Power of CAPS to Detect Changes in Arrhythmic Death Mortality (Assuming 4.5% Arrhythmia Death Rate)

Ratio of Treatment to Placebo Mortality	Power to Detect Difference (%)
Placebo Better Than Drug	
5.00	5.9
2.50	3.2
1.67	1.7
1.25	0.9
Drug Better Than Placebo	
0.80	0.9
0.60	1.7
0.40	3.2
0.20	5.9
0.10	8.1
0.05	9.5

See text for explanation. Calculation assumptions: 3.5%; arrhythmic death rate, α error = 0.013; sample size = 200, drop-in −0.02; drop-out −0.20.
CAPS = Cardiac Arrhythmia Pilot Study.

and placebo reached the CAPS efficacy goal in 37% of patients. Of the 4 limbs of active antiarrhythmic therapy, encainide, flecainide and moricizine were well tolerated compared with the placebo group. In addition, nearly 75% of the patients who began therapy with any of these 3 drugs continued to take them for the entire year. Imipramine had an undesirable toxicity profile compared with placebo.[15]

The results of the CAPS supported the feasibility of performing a full-scale clinical trial designed to test the hypothesis that VPC suppression in survivors of acute MI could reduce the incidence of arrhythmic sudden death. Regarding toxicity, proarrhythmia rates did not appear to differ between the encainide/flecainide groups and placebo. However, flecainide-treated patients had more congestive heart failure, whether compared with all other CAPS patients or only with placebo.[18] The cumulative incidence of arrhythmic death/cardiac arrest in CAPS was 4.5% in 1 year, a figure used to estimate the CAST sample size.[1,15]

Patients in the CAPS who were taking concomitant calcium channel blockers were more likely to develop congestive heart failure (18%) than those not receiving such therapy (8%, $p < 0.005$). There was a clear relation between the development of congestive heart failure and the baseline left ventricular ejection fraction (LVEF) for all therapies, including placebo.[18] For example, in the small subset of patients whose LVEF ranged between 20 and 29%, class III congestive heart failure occurred in 31% of patients taking encainide, 38% taking flecainide, 36% taking imipramine, 23% taking moricizine, and 17% taking placebo. Most of the patients who had worsening of congestive heart failure had it within the first 3 months of therapy.[18] The results of CAPS implied that there was a more negative inotropic effect of flecainide than encainide even though these drugs closely share electrophysiologic properties. Both were potent suppressors of VPCs, although all drugs tested were less effective in patients with an LVEF <30%.

Important observations were made from the CAPS placebo group. Holter-documented arrhythmia suppression often occurred in the CAPS placebo population. In fact, 37% of patients randomized to the CAPS placebo group had ≥70% VPC suppression by the end of drug dosing. This was a confounding variable, requiring consideration in planning the full-scale trial to test the hypothesis that VPC suppression could reduce sudden death. The CAPS, consistent with previous studies, documented a large daily VPC variability so that patients could appear to have VPC suppression or proarrhythmia due to intrinsic VPC variability, alone.[16,19]

STATISTICAL CONSIDERATIONS (LIMITATIONS IN DETECTING SERIOUS TOXICITY)

Based on the observed 364% increase of the primary CAST end point (arrhythmic death/cardiac arrest) in the encainide/flecainide group,[1] a valid question could be: Why couldn't the CAPS (a 502-patient pilot study) detect the magnitude of the toxicity of encainide and flecainide? Obviously the CAPS was not constructed to be a mortality trial but rather a pilot study to gather information useful in planning a full-scale mortality trial. The CAPS trial comprised 5 treatment groups of approximately 100 patients each, and the 1-year mortality in each group was relatively small (6 to 14%). Table III shows the relation between the ratio of placebo and active drug mortality rates and the power of the CAPS to detect some given drug effect on the incidence of arrhythmic death. The power of a study is the study's ability to detect the treatment effect of interest through the background variability or "noise" created by the different reactions of individual patients. Large clinical trials are designed to detect treatment effects with high power (usually a power greater than 0.80). Table III shows that the CAPS had little ability to detect a treatment effect (even a 2.5 to 3.6 times increased mortality) with any statistical certainty. In the CAST, the sudden death rate in the encainide/flecainide group exceeded that of placebo by 364% (33 of 730 vs 9 of 725 = 3.64). As shown in Table III, the ability of the CAPS to determine this increased mortality rate in either the encainide or flecainide groups compared with placebo was less than 5 chances in 100. It is clear from Table III that the CAPS, as a pilot study, could not possibly be expected to detect even large mortality differences between such small groups with statistical certainty. Were the CAPS to have actually demonstrated a five- or 10-fold increase in arrhythmic mortality with encainide or flecainide (which it did not) statistical analysis would, of course, show it to be a significant difference.

CAST DESIGN CONSIDERATIONS

The CAST was designed to test the hypothesis that suppressing VPCs in patients surviving acute MI would reduce the incidence of arrhythmic death/cardiac arrest (the primary end point). The CAST was designed and implemented in 1986. Many of the design features in the CAST are outlined in Table II. The CAST was similar to the CAPS in that it was double-blind with a parallel

placebo group. The VPC entrance criterion was slightly reduced to ≥6 VPCs/hour, LVEF limits were changed, and the entrance window from infarction was increased to 2 years. However, patients presenting later (from 91 days to 2 years) required an LVEF ≤40%. Based on information regarding the large arrhythmia variability from the CAPS,[16,19] the arrhythmia suppression goal of the CAST was more stringent. The definitions of VT and proarrhythmia were liberalized (Table II). Encainide, flecainide and moricizine were chosen for the CAST in doses that appeared to be safe in the CAPS, the goal being to provide alternative therapies so as to achieve VPC suppression in as many patients as possible. Based on the CAPS observation that flecainide increased the incidence of congestive heart failure, flecainide could only be randomly assigned to patients with an LVEF ≥30%. Because of superior VPC suppression in the CAPS, encainide or flecainide were the first choice in CAST patients whose LVEF was ≥30%.

Whereas many of the CAST design features were similar to the CAPS, there were 2 major differences. First, the CAST was designed to include only patients who demonstrated VPC suppression. Thus, patients were eligible for randomization only if they reached the ≥80% VPC suppression goal while receiving open-label encainide, flecainide or moricizine. Thus, as opposed to the CAPS, the CAST was a trial only of arrhythmia suppressors (i.e., "responders"). The presence of an open-label titration phase was the second major departure from the CAPS. The open-label phase in the CAST typically lasted approximately 2 weeks, the time it usually took to document arrhythmia suppression.

The CAST sample size estimate required 4,400 patients be followed for an average of 3 years. The primary end point, arrhythmic death/cardiac arrest, was assumed to have a 3-year cumulative incidence of 11% in the placebo group. This was extrapolated from the observed 1-year incidence of arrhythmic death/cardiac arrest in the CAPS, which was 4.5%, a rate thought likely to decrease in the second and third years. It was estimated that use of antiarrhythmic therapy could reduce the incidence of sudden cardiac death by 30%. The type I or α error was set at a 1-tail level of 0.025. The power of the study to detect the hypothesized difference in mortalities between the 2 groups was 0.84. Other considerations (e.g., drop-ins and drop-outs) resulted in the need to randomize 2,200 patients to each group (placebo vs antiarrhythmic therapy). The CAST trial was due to be completed both in enrollment and follow-up by 1992, when the results were to be unblinded and analyzed.[1]

UNEXPECTED MORTALITY INCREASE IN THE CAST ENCAINIDE/FLECAINIDE GROUP

As in all NHLBI clinical trials, an outside Data and Safety Monitoring Board objectively surveyed the CAST periodically for any unforeseen safety problems. During a routine analysis, the board discovered that the encainide/flecainide groups had an increase in both total (250%) and arrhythmic death (364%) mortality. Analysis of the baseline characteristics of the 1,455 patients randomized either to encainide/flecainide or their matching placebos showed no differences in prerandomization risk to explain the observed differences in mortality. The mortality figures were striking: of the 78 deaths in the 1,455 patients during the 10-month mean follow-up, 56 occurred in the encainide/flecainide group compared with 22 patients in the placebo group. Of the 42 arrhythmic deaths/cardiac arrests, 33 occurred in the encainide/flecainide group.[1] Relevant baseline characteristics and mortality results in the encainide/flecainide limb of the CAST compared with their placebo group are summarized in Table IV with the CAPS placebo group presented for reference. In general, patients in the CAST had lower mean LVEFs, more patients had an LVEF <40%, and β-blocking therapy was administered less often, but calcium channel blockers were given more frequently in the CAST than in the CAPS.

TABLE IV Comparison of Some Baseline Characteristics and Mortality Results in CAPS and CAST

	CAPS Placebo Group (n = 100)	CAST ENC/FLEC (n = 730)	CAST Placebo (n = 725)
Age (year)	60	61	61
Mean LVEF (%)	45	40	39
% with LVEF <40%	33.0	47.0	47.6
% with hx of angina	42.0	45.9	45.5
% with previous MI	31.0	34.9	37.6
% with diabetes mellitus	17.0	19.8	20.4
% on β blockers	41.0	30.4	33.1
% on CA blockers	34.0	52.3	49.3
% on digitalis	20.0	21.2	18.5
% on diuretics	30.0	31.6	31.8
% with runs of VT	32.0	21.2	20.1
% with hx of CHF	6.0	13.7	11.5
Total mortality (1 yr) (%)	9.0*	9.2†	3.6†
Sudden death mortality (1 yr) (%)	4.6†	5.4†	1.5†
Thrombolytic therapy (%)	17.0	28.2	24.3
CABG/PTCA (%)	18.0	53.6‡	54.1‡

* Calculated from entire CAPS population (n = 502).
† Extrapolated from 10 months to 1 year for comparison purposes (10-month mortality × 12/10 = 1 year mortality).
‡ Includes CABG/PTCA before qualifying infarct and after randomization.
CA = calcium; CABG = coronary artery bypass graft; CHF = congestive heart failure; ENC = encainide; FLEC = flecainide; hx = history; PTCA = percutaneous transluminal coronary angioplasty; other abbreviations as in Table II.

The most striking features of the CAST results were (1) the incredibly low arrhythmic death rate in the CAST placebo group, and (2) the appalling total and arrhythmic death mortality excess in the encainide/flecainide groups. These 2 issues merit detailed discussion.

DILEMMA OF THE LOW PLACEBO MORTALITY

The comparisons of the CAPS and the CAST study designs (Table II) and baseline characteristics (Table IV) would intuitively lead one to expect that the CAST placebo patients should have had a higher arrhythmic death incidence than that observed in the CAPS, because more patients in the CAST had lower LVEFs and a higher incidence of congestive heart failure. The extraordinarily low incidence of arrhythmic death in the CAST placebo

TABLE V Risk of Sudden Death Based on VPCs Detected on Holter Recording in Patients Surviving Acute Myocardial Infarction

Trial	Sample Size	Arrhythmic Death Mortality (%)	Total Mort.* (1 yr) (%)	Actual Follow-Up (mo)
CAST[1] (≥6 VPCs/hr)				10
Encainide/ Flecainide	730	5.4†	9.2†	
Placebo	725	1.5	3.6	
CAPS[15] (≥10 VPCs/hr)				12
All pts.	502	4.6	9.0	
Placebo	100	—	7.0	
Bigger et al[2]				24
All pts.	819	3.8	5.9	
0 VPC	112	1.5	3.0	
>3 VPCs/hr	245	6.1	9.8	
>10 VPCs/hr	162	6.3	9.4	
>30 VPCs/hr	89	7.0	10.5	
BHAT[7] (placebo group)				25
0 VPC	260	1.2	2.5	
Any VPC	1,380	2.6	5.5	
>10/hr	211	4.5	10.0	
<10/hr	1,429	2.0	4.3	
Moss et al[4]	759	6.8	11.0	6
Ruberman et al[3]				24
<10 VPCs/hr	1,285	2.3	6.4	
>10 VPCs/hr	454	7.6	13.6	

* All corrected to an estimated 1-year mortality.
† End point of death/cardiac arrest.
Mort. = morality; other abbreviations as in Tables I and II.

group (1.2% in 10 months, extrapolated to 1.5% for 1 year) not only is miniscule compared with the CAPS placebo group but also with other published experience. Table V summarizes the risk of arrhythmic death of patients surviving acute MI stratified for the extent of ventricular arrhythmia on Holter recordings.[1–4,7,15] In the study by Bigger et al,[2] the only arrhythmic death mortality approaching the low CAST placebo rate was in patients who had no VPCs on 24-hour Holter recording. In that trial, patients with ≥3 VPCs/hour (a lower entrance criterion than in the CAST) had a 6% annual arrhythmic death rate.[2] A similar annualized arrhythmic death rate was found if the VPC cutoff was ≥10 or ≥30 VPCs/hour. The Beta Blocker Heart Attack Trial (BHAT) placebo group with no VPCs paralleled the CAST placebo group, with a 1.2% annualized incidence of arrhythmic death.[7] In the trial by Ruberman et al,[3] the 454 patients with ≥10 VPCs/hour had a 7.6% annualized arrhythmic death rate. Thus, the CAST had a unique placebo group; although it was designed to reflect an increased risk for arrhythmic death, the 1-year arrhythmic death mortality behaved more like the lowest post-MI risk group possible (Table V).

WHY WAS CAST PLACEBO MORTALITY SO LOW?

There are many possible explanations for the low CAST placebo mortality. First, many high-risk patients were excluded (severe congestive heart failure, class IV angina, blood pressure ≥180/120 mm Hg, patients with sustained VT, QRS >0.18, high-degree heart block, severe hypotension). Because those exclusions were similar to those in the CAPS, other explanations must be found. Observations by Moss et al[4] over a decade ago showed that the risk of arrhythmic death in the first 6 months after acute MI primarily occurs in the first 1 to 2 months. In the 6-month follow-up study by Moss et al,[4] 59% of the arrhythmic deaths occurred within the first 2 months after MI. The open-label phase of the CAST (not present in the CAPS), required to identify patients who were responders, lasted approximately 2 weeks; during this interval, a number of deaths occurred, lost to the study mortality analysis. In fact, 62 of 2,315 patients died during the open-label titration phase. However, incorporation of these deaths into the CAST would probably not have led to a different conclusion. A reasonable assumption regarding these prerandomization deaths could be that had they occurred after randomization they might have been distributed equally across treatment groups (although it is more likely that excessive deaths would have occurred in the encainide/flecainide groups). If this was the case, the trend toward increased deaths in the treatment group is blunted but not reversed. Thus, the placebo arrhythmic death rate would have increased, more closely approximating previous published experience.

A second potential explanation for the low placebo mortality is that the CAST was designed only to enroll patients whose VPCs and nonsustained VT were suppressed. Identifying and enrolling only "suppressors" or "responders" may select a population with a low risk of arrhythmic death. Perhaps being a drug responder in the CAST is a powerful predictor of a good outcome and minimizes the arrhythmic death risk. This is a fascinating hypothesis that merits further research. Wellens et al[20] contributed an interesting commentary regarding patients with life-threatening VT undergoing programmed electrical stimulation. Whereas patients who have inducible sustained monomorphic VT apparently have a high risk of arrhythmic death, it has been presumed that if antiarrhythmic drugs inhibit this inducibility then patients should be discharged on that drug. While proposing a new approach to testing the validity of a programmed electrical stimulation hypothesis, a similar possibility analogous to CAST exists. Perhaps, as in the CAST, the observation that a patient can be rendered noninducible with an antiarrhythmic drug during programmed electrical stimulation is, in itself, an indicator of better prognosis.

Another explanation of the low placebo mortality in the CAST may be related to other differences in the medical management of the CAST compared with the CAPS placebo populations. Patients were randomized into the CAPS between 1983 and 1985. The CAST population comprised patients randomized from June 1987 through April 1989. During those 6 years, therapy for acute MI had changed dramatically, so that by the end of the decade a larger number of patients were receiving thrombolytic therapy and more patients were undergoing percutaneous transluminal coronary angioplasty (Table

IV). The majority of the increase in invasive procedures noted between the CAPS and the CAST placebo groups (Table IV) is accounted for by more frequent performance of percutaneous transluminal coronary angioplasty. Whether the combination of more thrombolytic therapy and more angioplasty further reduced the mortality in the CAST placebo group is speculative. However, the recent report from the Thrombolysis and Myocardial Infarction Trial (TIMI II) of patients with acute MI treated with tissue plasminogen activator followed by various strategies using percutaneous transluminal coronary angioplasty has shown a 42-day post-MI mortality of only 4.7%, a low mortality figure that includes all of the in-hospital mortality.[21] The TIMI II trial did not have a parallel placebo group, but this is an extraordinarily low combined in-hospital and early follow-up mortality. Whether differences in the percentage of patients taking β blockers or calcium channel blockers had any effect on the lower CAST placebo mortality is speculative. However, if anything, one would have expected a higher CAST placebo arrhythmic death rate since a lower percentage of the CAST patients were taking β blockers compared with the CAPS (Table IV).

WHY DID ENCAINIDE/FLECAINIDE INCREASE CAST MORTALITY?

The CAPS trial was underpowered to detect an increased mortality in the encainide/flecainide groups compared with placebo. A large number of published studies indicate that these electrophysiologic type IC antiarrhythmic drugs have a significant proarrhythmic potential and also may lead to an increase in left ventricular dysfunction (a second mechanism to increase mortality).

PROARRHYTHMIC POTENTIAL OF ANTIARRHYTHMIC DRUGS

The fact that antiarrhythmic drugs may actually provoke life-threatening ventricular arrhythmias has been recognized for over a quarter of a century.[22] Likewise, the negative inotropic potential of certain antiarrhythmic drugs has been documented for over a decade.[23] In their landmark study of 9 antiarrhythmic drugs used to treat patients with malignant ventricular arrhythmias, Velebit et al[24] reported aggravation of existing or provocation of new ventricular arrhythmias (frequently termed proarrhythmia) in 5 to 17% of drug experiences. In 63 patients with a history of malignant sustained ventricular arrhythmias, Poser et al[25] determined that 12.9% of the drug trials resulted in arrhythmia aggravation. Other investigators have identified a variety of proarrhythmic responses during programmed electrical stimulation testing of antiarrhythmic drugs. Horowitz et al[26] documented the conversion of nonsustained to sustained VT in 17% of their patients, and also identified an additional 12% of their population in whom the induction of sustained VT required a less aggressive stimulation protocol. A more recent report has documented new inducible sustained VT in 28% of 314 patients with sustained or nonsustained VT or ventricular fibrillation who were undergoing 801 drug studies.[27]

Proarrhythmic and negative inotropic effects of encainide: A recent analysis of the arrhythmogenic effects of antiarrhythmic drugs during programmed electrical stimulation has been reported by Stanton et al.[28] In this trial, arrhythmogenic effects occurred in 6.9% of 506 consecutive patients undergoing a total of 1,268 antiarrhythmic drug trials for VT or ventricular fibrillation. The highest reported incidence of proarrhythmia occurred with encainide (11.8%).[28] Winkle et al[29] reported similar observations over 9 years ago. In a group of patients with life-threatening arrhythmias, encainide frequently caused a polymorphic VT resulting in cardiac arrest. Similarly, Rinkenburger et al[30] noted that encainide frequently converts nonsustained to sustained VT and that most patients in whom sustained VT develops while taking encainide have substantial hypotension.[30] These reports refer mostly to patients with life-threatening ventricular arrhythmia and include less severe proarrhythmia, not limited to arrhythmic death.

Encainide also has a significant negative inotropic effect. The results of the CAPS failed to show any clinically significant increase in congestive heart failure with encainide compared with placebo.[15,18] In this respect, encainide appeared superior to flecainide, to the extent that the CAST patients with an LVEF <30% could be randomized to encainide. However, it is possible that the inability to show a significant negative inotropic effect of encainide in the CAPS was either a reflection of the patient population tested or simply a type II or β error. In a recent report by Gottlieb et al,[31] a single dose of 50 mg of encainide was given to 30 patients with severe symptomatic congestive heart failure, all of whom had an LVEF <40%. Invasive hemodynamic measurements were obtained using a balloon-tipped thermodilution catheter. Within 2 hours after its administration, encainide produced a significant deterioration of multiple hemodynamic variables, including cardiac index and stroke work index, and an increase in pulmonary capillary wedge pressure.[31] In 8 of the 30 patients, the documented negative inotropic effects were accompanied by worsening symptoms of congestive heart failure. As opposed to the results of the CAPS, administration of encainide to patients with symptomatic left ventricular dysfunction definitely appears to cause hemodynamic deterioration.[31] The negative inotropic effect of encainide may have impacted on CAST, where 40% of the encainide/flecainide group had an initial LVEF <40% and encainide was given to CAST patients with an LVEF <30%.

Proarrhythmic and negative inotropic effects of flecainide: A review of flecainide toxicity shows a similar pattern of toxicity to encainide. The results of the CAPS have shown that patients with relatively modest left ventricular dysfunction have further symptomatic deterioration of left ventricular function during flecainide therapy.[15,18] Multiple studies have documented the potential of flecainide to induce life-threatening ventricular arrhythmias. In a review of the flecainide database, Morganroth et al[32] pointed out that the presenting arrhythmia is predictive in determining which patients are more likely to have a proarrhythmic effect with flecainide therapy. Pa-

TABLE VI Confounding Variables When Assessing or Comparing Efficacy/Safety of Antiarrhythmic Drugs Using Published Reports

1. Assorted patient populations (asymptomatic VPCs, post-MI, cardiomyopathy, congestive heart failure)
2. Patients with new onset arrhythmia vs patients previously refractory to therapy
3. Various presenting arrhythmias, varying definitions of sustained VT
4. Lack of baseline quantitative LVEF in some trials/patients
5. Different suppression end points
6. Different evaluation modalities (Holter, programmed electrical stimulation)
7. Various durations of Holter recording, different electrophysiologic stimulation protocols
8. Different drug doses, dosing intervals
9. Different durations of study to assess outcome (from acute drug testing to chronic oral therapy)
10. Different drug sequences (first choice or last resort?)
11. Lack of mortality end points
12. Lack of parallel placebo group

Abbreviations as in Table II.

tients presenting with symptomatic sustained VT are much more likely to have a proarrhythmic death associated with flecainide (3.1% of patients) than patients presenting with nonsustained VT or with benign VPCs (0.2 and 0% incidence of proarrhythmic deaths, respectively; $p < 0.01$).[32] The mean observation period of the flecainide database (1,330 patients followed for a mean of 292 days) is nearly identical to CAST (300 days); yet Morganroth et al[32] reported only a 0.2% incidence of proarrhythmic death for patients in the potentially lethal category. In their experience with 55 consecutive patients treated with oral flecainide, Anastasiou-Nana et al[33] noted that 7 of these patients (13%) had new or more sustained exercise-induced ventricular arrhythmias or a new wide-complex VT. Similar reports of the proarrhythmic effects of flecainide have appeared in multiple publications.[34,35]

In an editorial reviewing the high incidence of encainide-induced proarrhythmia during electrophysiologic testing reported by Stanton et al,[28] Sheinman[36] commented on his own experience, concluding that there is a high incidence of proarrhythmia with encainide in patients with life-threatening arrhythmia, such that type IC agents should not be used in the management of patients with severe organic heart disease and a history of sustained VT or ventricular fibrillation. Most previous reports of proarrhythmia or arrhythmia aggravation and provocation previously mentioned involve patients with lethal ventricular arrhythmias (patients presenting with sustained VT, ventricular fibrillation and sudden cardiac death).

It is difficult to extrapolate observations made from patients with lethal ventricular arrhythmias to patients with asymptomatic ventricular arrhythmias surviving acute MI, such as those found in the CAST population (frequently termed potentially lethal). Our recent report of a group of 246 patients (recent MI excluded) treated with a variety of antiarrhythmic agents (procainamide, quinidine, disopyramide, cifenline, moricizine, indecainide, metoprolol and sotalol) provides an ominous and consistent warning about antiarrhythmic drug administration to the potentially lethal arrhythmia category.[37] Using arrhythmia suppression criteria similar to those found in the CAPS and the CAST, we found that only 82 of 246 patients (33%) maintained adequate arrhythmia suppression for 2 weeks. Patients with an LVEF >40% maintained arrhythmia suppression more frequently ($p = 0.04$). Serious complications of antiarrhythmic drug therapy occurred most frequently in the 61 patients with an LVEF <30% (15 vs 2.1%, $p = 0.005$). The frequency of patients developing sudden cardiac death or congestive heart failure while taking antiarrhythmic therapy within 2 weeks was 8 times more frequent in patients with an LVEF <30% ($p = 0.003$).[37] Our data suggest that even in the patient population with asymptomatic or mildly symptomatic potentially lethal ventricular arrhythmias, VPC suppression often is not maintained for even 2 weeks, is of unproved benefit, and is itself potentially lethal. Based on our study, we believe that a treatment strategy of arrhythmia suppression is not justified in this population until it is shown to improve prognosis, as the risk is substantial and the benefit of arrhythmia suppression has not been proved.[37] Our data emphasize the importance and validity of the approach taken in the CAST.

In his review of the databases from both flecainide and encainide, Morganroth[38] concluded that proarrhythmic events are much more likely to occur in the setting of structural heart disease, sustained VT, inpatient initiation of therapy, and large-dose escalation of class IC drugs. What is not so clear is why, given the large experience in the 2 United States databases (flecainide, n = 1,330; encainide, n = 1,755), was such a large proarrhythmia not previously detected or at least suspected? After all, this combined experience (>3,000 patients) exceeds the size of the CAST encainide/flecainide group fourfold. The CAST population was classified as a potentially lethal group; yet the CAST encainide/flecainide population had a 7.7% total mortality and 4.4% arrhythmic death mortality at 10 months, higher than reported even for lethal arrhythmias from the drug database observations.[38]

The explanation for this large mortality discrepancy is complex and emphasizes the importance of the study design of the CAST. A number of confounding variables (Table VI) make comparison of various antiarrhythmic drugs (safety or efficacy) impossible. A major difference from the CAST in the large flecainide/encainide pharmaceutical experience was that recent survivors of acute MI were almost always excluded except for individual "emergency use" circumstances. The CAST population was a post-MI group and thus contained many patients with symptomatic and silent myocardial ischemia. There is another important comparative point. In the flecainide database (n = 1,330) experience, 13 of the 14 sudden deaths attributed to flecainide occurred in <14 days, a commonly used cutoff, beyond which a drug is usually not considered proarrhythmic. Minardo et al[39] likewise considered drug-associated ventricular fibrillation to be an early event (mean 3 days). In contrast, arrhythmic

deaths in the CAST encainide/flecainide group occurred at an increased rate throughout the 10 months compared with the placebo group.[1] This observation challenges our conventional wisdom regarding proarrhythmia, suggesting that new mechanisms leading to arrhythmic death may be involved. The last 2 design issues (nos. 11 and 12) listed in Table VI were corrected by the CAST, thus allowing the detection of this increased mortality.[1] These design features of the CAST amplify the extraordinary power of a parallel placebo group to detect an unexpected mortality end point.

SUGGESTED MECHANISM OF ENCAINIDE/FLECAINIDE PROARRHYTHMIA IN CAST

It has been suggested that the mechanism by which antiarrhythmic drugs induce life-threatening ventricular arrhythmias is their electrophysiologic effect of slowing conduction in diseased myocardium, potentially enhancing the possibility of reentrant VT.[29] Rinkenberger et al[30] postulated that antiarrhythmic drugs may facilitate the initiation of sustained VT by prolonging activation time while only increasing refractoriness minimally, effects that might be accentuated during acute ischemia. Relevant to this point, Nattel et al[40] established that pretreatment with aprindine, in a canine infarct model, greatly increases the incidence of sustained VT during acute ischemia compared with no pretreatment. Thus, pretreatment with an antiarrhythmic drug before coronary occlusion was "proarrhythmic"; the investigators attributed this to the delayed disappearance of aprindine from the ischemic zone compared with nonischemic zones.[40]

In a separate trial, Garan et al[41] used the 2-week-old canine MI model and showed that the induction of 10 minutes of reversible myocardial ischemia increases the incidence of spontaneous ventricular fibrillation from 13 to 54% when comparing dogs who had sham operations with those with permanent left anterior descending coronary artery occlusion (i.e., after infarction). Perhaps this decreased fibrillation threshold during acute ischemia in the presence of old infarction is enhanced by the presence of certain antiarrhythmic agents in humans as well. In the CAST, the risk ratio in the encainide/flecainide-treated patients with previous infarction was much higher than those without a previous infarct (risk ratio = 5.1 with and 2.1 without prior MI vs placebo).[1] Patients randomized in the CAST did not have any systematic baseline measurement of exercise-induced ischemia, making retrospective assessment of that risk factor difficult. But clearly, traditional concepts of proarrhythmia (occurring very early in sicker patients) do not fit the CAST observations and require a fresh look at our preconceptions. Animal models (especially the healed infarct model with induced ischemia)[41] seem an ideal fertile soil for new conceptual growth and a reasonable area in which to conduct (perhaps require?) antiarrhythmic drug testing.

CONTINUATION OF CAST

Do the results of the CAST prove that there is no benefit to arrhythmia suppression in patients with ventricular arrhythmia surviving acute MI? This is clearly not the message of the interim results of the CAST. Although VPC suppression may be necessary to reduce arrhythmic death in patients like those in the CAST, alone, it is not necessarily sufficient. The CAST is continuing to enroll patients to test the VPC suppression hypothesis with antiarrhythmic drugs other than the type IC agents (currently, moricizine, and perhaps adding others). It is clear from the previous discussion that a fairly large body of information has been accumulated about the risk of encainide and flecainide. Thus, the possibility exists that this mortality increase is unique to the type IC agents.

TABLE VII Power and Sample Size Computations for Varying Placebo Mortality Rates

3-Year Placebo Arrhythmic Death Rate	Power with n = 4400	Sample Size with Power = 0.85
0.040	0.428	12484
0.045*	0.468	11165
0.050	0.507	9752
0.054	0.557	8650
0.059	0.604	7986
0.064	0.636	7222
0.069	0.667	6589
0.073	0.714	6190
0.078	0.740	5834
0.083	0.771	5407
0.088	0.800	5038
0.092	0.819	4795
0.097	0.842	4499
0.102†	0.863	4235

* CAST (observed).
† CAST (predicted) (see text for discussion).
Assumptions: desired efficacy = 30%; 1-sided p α = 0.025; 3-year follow-up.

Based on the interim analysis of the placebo group in the CAST, it would have been difficult for any antiarrhythmic drug to show a clear benefit compared with placebo in reducing arrhythmic death mortality. It is difficult to reduce a 1.2% arrhythmic death rate at 10 months. Table VII presents the power and sample size computations for a range of placebo mortality rates over the projected 3-year follow-up period of the CAST. If patients taking placebo only have an arrhythmic death rate of 1.5% in 1 year (the reported CAST result extrapolated from 10 months to 1 year), a 30% treatment benefit could only be detected with a power of 0.48 in a trial of 4,400 patients. Conversely, a clinical trial would require a sample size of 11,165 patients to detect a 30% reduction in arrhythmic death with a power of 0.85 if arrhythmic deaths occurred only at a 1.5% annual rate for 3 years. Thus, the unanticipated low placebo mortality rate led to the underpowering of CAST, crippling its ability to detect the treatment difference for which it was designed.

As a result, a number of changes in eligibility criteria have been incorporated into the CAST in order to randomize patients at higher risk. Although the qualifying arrhythmia remains the same, LVEF must be lower (≤40%), the open-label titration phase (in which there was a large loss of analyzable mortality) has been changed to incorporate a placebo group, and the CAPS

entry window has been narrowed to the high-risk period (<90 days). These alterations in the CAST study design should allow for the detection of a 30% reduction in arrhythmic death if arrhythmia suppression by other antiarrhythmic drugs is truly beneficial in the CAST population.

CLINICAL IMPLICATIONS OF CAST

Perhaps we should incorporate long-held knowledge about risk stratification after MI to our clinical approach to arrhythmias: i.e., that the risk of arrhythmic death is related to the ventricular arrhythmia, left ventricular function and detectable myocardial ischemia. A unified research effort and clinical approach is necessary (perhaps we should become "lumpers" rather than "splitters"). A myopic view focused on arrhythmia evaluation and suppression without optimally treating both ischemia and left ventricular dysfunction has thus far not proved beneficial. Clinicians should consider a comprehensive strategy that addresses all 3 risk areas, with a healthy skepticism of using antiarrhythmic agents in patients similar to those in the CAST.[1,37]

The CAST documents that patients with VPCs post-MI who are ≥90 days after infarct or whose LVEF is preserved have a low arrhythmic death risk. Other than β blockers, antiarrhythmic drugs should not be given to such asymptomatic patients. The CAST results cannot be extrapolated to support such a pessimistic approach in symptomatic patients or in those with sustained VT or a history of cardiac arrest in whom drug therapy is useful, and drug selection should be performed using programmed electrical stimulation.

What should the clinician do with patients presenting with complex ventricular arrhythmias and left ventricular dysfunction who have survived acute MI? The only proved beneficial therapy is the use of β blockers (propranolol, timolol, metoprolol and atenolol).[8–12] Unfortunately, many such patients cannot tolerate β blockers. Not only is antiarrhythmic therapy of unproved benefit in this population, but also the type IC agents have increased sudden death mortality. The empiric use of antiarrhythmic drugs other than β blockers in this group is therefore not warranted.[1,37] The continuation of the CAST offers the best hope for obtaining objective information that may identify a successful treatment strategy in this population, which remains at increased risk for arrhythmic death.

REFERENCES

1. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med 1989;321:406–412.*

2. Bigger JT, Fleiss JL, Kleiger R, Miller JP, Rolnitzky LM, and the Multicenter Post-Infarction Research Group. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. *Circulation 1984;69:250–258.*

3. Ruberman W, Weinblatt E, Goldberg JK, Frank CW, Shapiro S. Ventricular premature beats and mortality after myocardial infarction. *N Engl J Med 1977;297:750–757.*

4. Moss AJ, DeCamilla J, Davis H. Cardiac death in the first 6 months after myocardial infarction: potential for mortality reduction in the early posthospital period. *Am J Cardiol 1977;39:816–820.*

5. Mukharji J, Rude RE, Poole WK, Gustafson N, Thomas LR Jr, Strauss HW, Jaffe AS, Muller JE, Roberts R, Raabe DS Jr, Croft CH, Passamani E, Braunwald E, Willerson JT, and The MILIS Study Group. Risk factors for sudden death after acute myocardial infarction: two-year follow-up. *Am J Cardiol 1984;54:31–36.*

6. The Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. *N Engl J Med 1983;309:331–336.*

7. Friedman LM, Byington RP, Capone RJ, Furberg CD, Goldstein S, Lichstein E, for the Beta-Blocker Heart Attack Trial Research Group. Effect of propranolol in patients with myocardial infarction and ventricular arrhythmia. *JACC 1986;7:1–8.*

8. Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA 1982;247:1707–1714.*

9. Furberg CD, Hawkins CM, Lichstein E, for the Beta-Blocker Heart Attack Trial Study Group. Effect of propranolol in postinfarction patients with mechanical or electrical complications. *Circulation 1984;69:761–765.*

10. Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med 1981;304:801–807.*

11. Hjalmarson A, Herlitz J, Malek I, Ryden L, Vedin A, Waldenstrom A, Wedel H, Elmfeldt D, Holmberg S, Nyberg G, Swedberg K, Waagstein F, Waldenstrom J, Wilhelmsen L, Wilhelmsson C. Effect on mortality of metoprolol in acute myocardial infarction: a double-blind randomised trial. *Lancet 1981;2:823–827.*

12. ISIS-I (First International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous atenolol among 16027 cases of suspected acute myocardial infarction: ISIS-I. *Lancet 1986;2:57–66.*

13. May GS, Eberlein KA, Furberg CD, Passamani ER, DeMets DL. Secondary prevention after myocardial infarction: a review of long-term trials. *Prog Cardiovasc Dis 1982;24:331–352.*

14. The CAPS Investigators. The Cardiac Arrhythmia Pilot Study. *Am J Cardiol 1986;57:91–95.*

15. The Cardiac Arrhythmia Pilot Study (CAPS) Investigators. Effects of encainide, flecainide, imipramine and moricizine on ventricular arrhythmias during the year after acute myocardial infarction: the CAPS. *Am J Cardiol 1988;61:501–509.*

16. Pratt CM, Theroux P, Slymen D, Riordan-Bennett A, Morisette D, Galloway A, Seals AA, Hallstrom A. Spontaneous variability of ventricular arrhythmias in patients at increased risk for sudden death after myocardial infarction: consecutive ambulatory electrocardiographic recordings of 88 patients. *Am J Cardiol 1987;59:278–283.*

17. Morganroth J, Michelson EL, Horowitz LN, Josephson ME, Pearlman AS, Dunkman WB. Limitations of routine long-term electrocardiographic monitoring to assess ventricular ectopic frequency. *Circulation 1978;58:408–414.*

18. Greene HL, Richardson DW, Hallstrom AP, McBride R, Capone RJ, Barker AH, Roden DM, Echt DS, and the CAPS Investigators. Congestive heart failure after acute myocardial infarction in patients receiving antiarrhythmic agents for ventricular premature complexes (Cardiac Arrhythmia Pilot Study). *Am J Cardiol 1989;63:393–398.*

19. Pratt CM, Hallstrom AP, Coromilas J, Romhilt DW, and the CAPS Investigators. Apparent "arrhythmia reduction" by antiarrhythmic therapy in postinfarction patients: a natural history of the placebo group in the Cardiac Arrhythmia Pilot Study (CAPS) (abstr). *Circulation 1986;74:857.*

20. Wellens HJJ, Brugada P, Stevenson WG. Programmed electrical stimulation of the heart in patients with life-threatening ventricular arrhythmias: What is the significance of induced arrhythmias and what is the correct stimulation protocol? *Circulation 1985;72:1–7.*

21. The TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction (TIMI) Phase II Trial. *N Engl J Med 1989;320:618–627.*

22. Selzer A, Wray HW. Quinidine syncope. *Circulation 1964;30:17–26.*

23. Podrid PJ, Schoenberger A, Lown B. Congestive cardiac failure caused by oral disopyramide. *N Engl J Med 1980;302:614–617.*

24. Velebit V, Podrid P, Lown B, Cohen B, Graboys TB. Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs. *Circulation 1982;65:886–894.*

25. Poser R, Podrid PJ, Lombardi F, Lown B. Aggravation of arrhythmia induced with antiarrhythmic drugs during electrophysiologic testing. *Am Heart J 1985;110:9–16.*

26. Horowitz LN, Greenspan AM, Rae AP, Kay RH, Spielman SR. Proarrhythmic responses during electrophysiologic testing. *Am J Cardiol 1987;59:45E–48E.*

27. Rae AP, Kay HR, Horowitz LN, Spielman SR, Greenspan AM. Proarrhythmic effects of antiarrhythmic drugs in patients with malignant ventricular arrhythmias evaluated by electrophysiologic testing. *JACC 1988;12:131–139.*

28. Stanton MS, Prystowsky EN, Fineberg NS, Miles WM, Zipes DP, Heger JJ. Arrhythmogenic effects of antiarrhythmic drugs: a study of 506 patients treated for ventricular tachycardia or fibrillation. *JACC 1989;14:209–215.*

29. Winkle RA, Mason JW, Griffin JC, Ross D. Malignant ventricular tachyarrhythmias associated with the use of encainide. *Am Heart J 1981;102:857–864.*

30. Rinkenberger RL, Prystowsky EN, Jackman WM, Naccarelli GV, Heger JJ,

Zipes DP. Drug conversion of nonsustained ventricular tachycardia to sustained ventricular tachycardia during serial electrophysiologic studies: identification of drugs that exacerbate tachycardia and potential mechanisms. *Am Heart J 1982;103:177–184.*

31. Gottlieb SS, Kukin ML, Yushak M, Medina N, Packer M. Adverse hemodynamic and clinical effects of encainide in severe chronic heart failure. *Ann Intern Med 1989;110:505–509.*

32. Morganroth J, Anderson JL, Gentzkow GD. Classification by type of ventricular arrhythmia predicts frequency of adverse cardiac events from flecainide. *JACC 1986;8:607–615.*

33. Anastasiou-Nana MI, Anderson JL, Stewart JR, Crevey BJ, Yanowitz FG, Lutz JR, Johnson TA. Occurrence of exercise-induced and spontaneous wide complex tachycardia during therapy with flecainide for complex ventricular arrhythmias: a probable proarrhythmic effect. *Am Heart J 1987;113:1071–1077.*

34. Nathan AW, Hellestrand KJ, Bexton RS, Banim SO, Spurrell RAJ, Camm AJ. Proarrhythmic effects of the new antiarrhythmic agent flecainide acetate. *Am Heart J 1984;107:222–228.*

35. Wehr M, Noll B, Krappe J. Flecainide-induced aggravation of ventricular arrhythmias. *Am J Cardiol 1985;55:1643–1644.*

36. Scheinman MM. Proarrhythmia and Primum Non Nocere (editorial). *JACC 1989;14:216–217.*

37. Pratt CM, Eaton T, Francis M, Woolbert S, Mahmarian J, Roberts R, Young JB. The inverse relationship between baseline left ventricular ejection fraction and outcome of antiarrhythmic therapy: a dangerous imbalance in the risk-benefit ratio. *Am Heart J 1989;118:433–440.*

38. Morganroth J. Risk factors for the development of proarrhythmic events. *Am J Cardiol 1987;59:32E–37E.*

39. Minardo JD, Heger JJ, Miles WM, Zipes DP, Prystowsky EN. Clinical characteristics of patients with ventricular fibrillation during antiarrhythmic drug therapy. *N Engl J Med 1988;319:257–262.*

40. Nattel S, Pedersen DH, Zipes DP. Alterations in regional myocardial distribution and arrhythmogenic effects of aprindine produced by coronary artery occlusion in the dog. *Cardiovasc Res 1981;15:80–85.*

41. Garan H, McComb JM, Ruskin JN. Spontaneous and electrically induced ventricular arrhythmias during acute ischemia superimposed on 2 week old canine myocardial infarction. *JACC 1988;11:603–611.*

A Perspective on Ventricular Arrhythmias: Patient Assessment for Therapy and Outcome

Albert L. Waldo, MD, Richard W. Henthorn, MD, and Mark D. Carlson, MD

Clinical management of patients with ventricular arrhythmias continues to evolve. It is generally accepted that patients with sustained ventricular tachyarrhythmias (ventricular tachycardia [VT] or fibrillation) require treatment. It is also generally accepted that patients with frequent or complex ventricular ectopy or nonsustained VT, in the absence of underlying heart disease, do not require treatment unless relief of symptoms is warranted. Whether patients with frequent or complex ventricular ectopy or nonsustained VT require treatment in the presence of underlying organic heart disease remains uncertain. The concern is that these ventricular arrhythmias may be a precursor for sustained, potentially life-threatening ventricular tachyarrhythmias. Available data suggest that patients with underlying heart disease, particularly coronary artery disease and a previous myocardial infarction, who manifest frequent or complex ventricular ectopy or nonsustained VT are at increased risk for sudden cardiac death. However, no studies have shown that treatment of these arrhythmias will affect outcome. Data are accumulating to suggest that use of the principles of risk stratification permits identification of patients at very high risk for developing sustained ventricular tachyarrhythmias. Carefully designed clinical trials are required before one can provide firm guidelines for the management of these patients. Nevertheless, when several risk factors for sudden cardiac death (e.g., abnormal ejection fraction, a late potential on a signal-averaged electrocardiogram, and frequent or complex ventricular ectopy or nonsustained VT) are present in a patient, especially after a recent myocardial infarction, invasive electrophysiologic testing may help identify those who need treatment (sustained VT is inducible) and those who do not (no sustained VT is inducible).

(Am J Cardiol 1990;65:30B–35B)

From the Department of Medicine, Case Western Reserve University and University Hospitals of Cleveland, Cleveland, Ohio. This study was supported in part by Grant R01 HL 38408 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; a Research Initiative Award from the Northeast Ohio Affiliate of the American Heart Association, and the Wuliger Foundation, Cleveland, Ohio.

Address for reprints: Albert L. Waldo, MD, Division of Cardiology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

Ventricular arrhythmias are a remarkably common phenomenon. They may occur in many forms, including ventricular premature complexes (VPCs) with variable frequency, nonsustained ventricular tachycardia (VT), sustained VT and ventricular fibrillation. These arrhythmias run the gamut from asymptomatic and benign to symptomatic and life threatening. The problem is knowing which ventricular arrhythmias warrant therapy and which do not.

VENTRICULAR TACHYCARDIA OR FIBRILLATION

Ventricular fibrillation is not compatible with life. In survivors of out-of-hospital ventricular fibrillation, the reported recurrence rate is 30 to 40% at 1 year.[1] Therefore, there is no question that this rhythm must be effectively treated when diagnosed.

Sustained VT (defined as a rhythm originating in the ventricles at a rate >100 beats/min and lasting ≥30 seconds, or <30 seconds if requiring intervention)[2] is almost always serious and potentially life threatening, especially when it occurs in the presence of underlying heart disease. It may be associated with marked hypotension or other intolerable symptoms, such as angina pectoris in patients with coronary artery disease. Furthermore, VT may be a precursor to ventricular fibrillation. Therefore, patients with sustained VT should be carefully evaluated, and an effective course of therapy established.[3]

VENTRICULAR ECTOPY OR NONSUSTAINED VENTRICULAR TACHYCARDIA

Whether or not frequent (≥6 VPCs/hour) or complex ventricular ectopy or nonsustained VT (defined as ≥3 VPCs in a row, up to 30 seconds, at a rate of 100 beats/min)[2] should be treated is not so clear. The concern is that these arrhythmias may act as a trigger or precursor for sustained, life-threatening ventricular tachyarrhythmias. Nevertheless, frequent or complex ventricular ectopy or nonsustained VT may also be benign. Distinguishing patients in whom these arrhythmias are benign from those in which the arrhythmias portend more serious consequences is a difficult problem.

WHICH PATIENTS NEED TREATMENT?

In the absence of underlying organic heart disease, frequent or complex ventricular ectopy or nonsustained VT are probably not associated with a significant incidence of serious or life-threatening ventricular arrhythmias.[4] In fact, because of the potential for drug-induced proarrhythmia in these patients, treating the arrhythmia

may pose a greater risk than no treatment. Proarrhythmic rhythms may include life-threatening VT or ventricular fibrillation. Therefore, for patients in this category, it is generally accepted that treatment with antiarrhythmic agents is best avoided unless relief of the symptoms warrants the risk of proarrhythmia.[1]

Epidemiologic background: The problem is in patients who present with frequent or complex ventricular ectopy or nonsustained VT in the presence of underlying organic heart disease, especially coronary artery disease with a previous myocardial infarction (MI). As summarized recently, numerous epidemiologic studies have shown that frequent or complex ventricular ectopy or nonsustained VT in patients with a prior MI are independent markers of an increased risk for sudden cardiac death.[5] This concern has influenced physician practice patterns,[6] and has generated numerous drug treatment trials. It has also led to the recent Cardiac Arrhythmia Pilot Study[5] and the Cardiac Arrhythmia Suppression Trial (CAST),[7] clinical trials designed to address the question of whether or not suppression of frequent or complex ventricular ectopy and nonsustained VT will affect outcome in patients with a recent MI.

Pathophysiologic background: Apart from the epidemiologic evidence, there is a pathophysiologic basis for these concerns. It is now well recognized that most life-threatening ventricular tachyarrhythmias are caused by reentrant rhythms. VT is usually due to so-called ordered reentry, and ventricular fibrillation to what is termed random reentry.[8] A trigger is almost always required for the initiation of reentrant rhythms. For ventricular tachyarrhythmias, the trigger is usually a VPC (or VPCs). Should the wave front from the VPC(s) encounter an area of unidirectional block, the wave front may travel around the area of block (Fig. 1). When the electrophysiologic (EP) and anatomic parameters are such that the impulse can travel around the block and reenter from the opposite side (usually via an area of slow conduction), the impulse can then generate a reentrant beat that, when it travels around the reentry circuit continuously, generates a tachycardia (Fig. 2). When multiple reentrant circuits are generated, fibrillation occurs.[9]

Understanding the pathophysiology of reentrant rhythms is also a prerequisite for understanding the basis of effective treatment of ventricular tachyarrhythmias. Theoretically, these life-threatening rhythms can be prevented by (1) suppressing the trigger(s) (e.g., with antiarrhythmic therapy); (2) affecting the EP parameters of the abnormal anatomic substrate so that it will no longer support a reentrant rhythm (e.g., with antiarrhythmic drug therapy or by ablating ventricular tissue responsible for generating the tachycardia, using either an electrode catheter technique or an open heart surgical procedure); or (3) surgically excising the abnormal anatomic substrate responsible for the reentrant circuit.

A major point in understanding the pathophysiology of serious or life-threatening ventricular tachyarrhythmias is that, hypothetically, if one suppresses the trigger(s), such arrhythmias may not be precipitated. Fur-

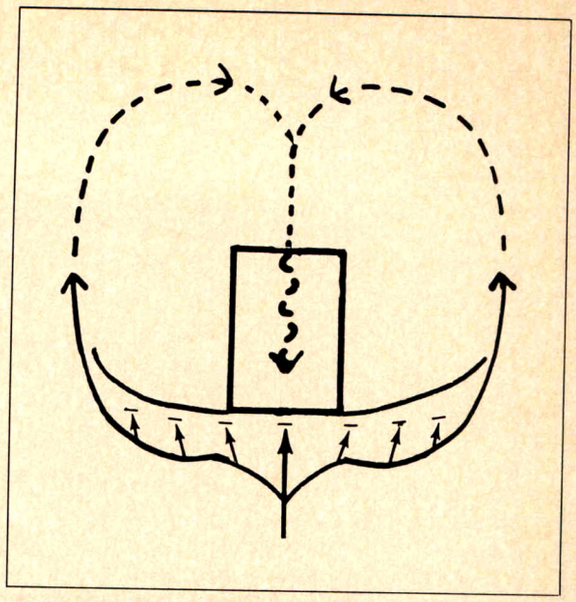


FIGURE 1. Representation of the onset of ventricular tachycardia due to reentry. A wave front from a premature beat (*solid arrows*) encounters an area of unidirectional block (*bars*). The wave front travels around both sides of the area of unidirectional block so that it subsequently activates the area behind the region of block after traveling through an area of slow conduction (*box*, the *dashed serpentine line* in the box indicating slow conduction of the wave front). Conduction around the region of unidirectional block, and then through the area of slow conduction, takes sufficiently long that when the activation wave front reaches the area of the original block (this time, from the opposite direction), the tissue on the other side of the block has had time to repolarize. The wave front then is conducted through the area of previous unidirectional block, initiating a sustained reentrant rhythm (see Fig. 2).

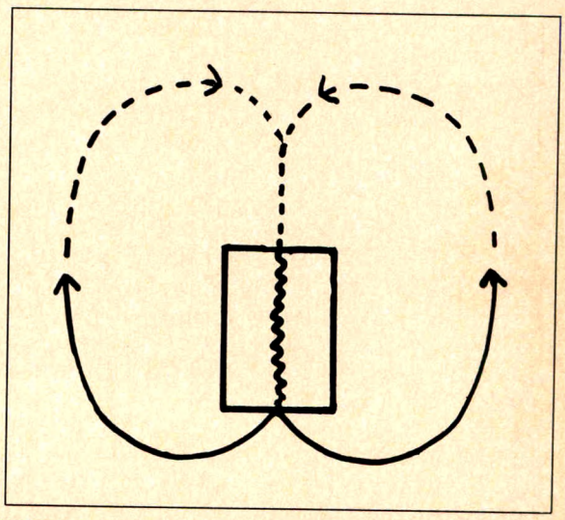


FIGURE 2. Representation of a figure-of-8 loop reentry circuit during sustained spontaneous ventricular tachycardia, the onset of which was illustrated in Figure 1. The area of unidirectional block is no longer illustrated, as the wave front has exited the area of slow conduction (*solid lines* with *arrow*) to travel around (reenter) the reentrant circuit. *Dashed lines* indicate the subsequent route of the reentrant wave front.

thermore, antiarrhythmic drug therapy used to suppress the trigger(s) may also favorably affect the abnormal anatomic substrate that had been supporting the reentry circuit. As reasonable and logical as this hypothesis is, it remains unproven.[10] Some studies have indicated that although antiarrhythmic drug treatment in such patients may protect against sudden cardiac death, it may also increase mortality. The CAST clearly showed that for patients with frequent ventricular ectopy (≥6 VPCs/hour) or nonsustained VT (≤14 beats in a row at a rate of ≥120 beats/min) and a recent MI (6 days to 2 years), treatment with either encainide or flecainide was associated with about a 3:1 risk ratio for death from arrhythmia or cardiac arrest, compared with a placebo-treated group.[7] Before the CAST, there was a hint of this potential outcome. A retrospective study by Rapaport and Remedios[11] of high-risk patients after recovery from MI showed that not only was complex ventricular ectopy a significant marker for mortality, but that mortality was higher in the patients who received antiarrhythmic drug therapy than in those who did not receive such therapy. In addition, 2 large, double-blind, placebo-controlled studies[12,13] to assess antiarrhythmic efficacy and tolerance of mexiletine in patients thought to be at risk for sudden cardiac death after MI showed significant suppression of ventricular ectopy in treated patients. However, there was an associated increased incidence (only a trend; not statistically significant) in mortality in those treated compared with placebo controls.

Ehlarrar et al[14] demonstrated that dogs treated with aprindine before creation of an acute MI have a significantly higher incidence of ventricular tachyarrhythmias than those that receive aprindine only after MI. The implication of this study is that myocardial ischemia or infarction in the presence of an antiarrhythmic drug may predispose to the very arrhythmia that the drug is meant to prevent.

The advent of aggressive thrombolytic therapy and early revascularization (angioplasty and coronary artery bypass graft surgery) to relieve ischemia may have altered the significance of ventricular ectopy or nonsustained VT after MI. The epidemiologic studies that identified VPCs or nonsustained VT as independent markers of an increased risk for sudden cardiac death may not be relevant in patients who undergo these therapies. Thus, new epidemiologic studies to assess the predictive value of frequent or complex ventricular ectopy or nonsustained VT as an independent marker of sudden cardiac death may be needed. In fact, the CAST may have given some indication of this, because death from arrhythmia or sudden cardiac arrest was only 1.2% in the placebo-treated patients. No patient who was treated with thrombolytic therapy died during qualifying MI, nor did any patient whose qualifying Holter monitor examination was obtained ≥90 days after MI.

How then does one decide which patients with ventricular ectopy or nonsustained VT should be treated? For patients with no associated organic heart disease, there is a sound basis for recommending no treatment unless warranted by symptoms. For patients with frequent or complex ventricular ectopy or nonsustained VT associated with organic heart disease, a group constituting most of those seen in clinical practice, no clear recommendation can be made. Although they may be at increased risk for sudden cardiac death, antiarrhythmic drug therapy has not been shown to reduce mortality in these patients.[10] The remaining problems are identifying those at high risk for developing a sustained ventricular tachyarrhythmic event and finding effective therapy that will improve outcome for such patients. It is anticipated that future studies will provide better solutions for these problems. Until then, all else is speculation. Nevertheless, it seems a valid assumption that some of these patients should be treated. A reasoned approach to defining which of these patients might benefit from antiarrhythmic therapy, based on available data for identifying patients at high risk for sustained ventricular tachyarrhythmia and sudden cardiac death, is offered in the next section.

RISK FACTORS FOR SUDDEN CARDIAC DEATH

In addition to associated organic heart disease, several other factors are predictors of sudden cardiac death in patients with frequent or complex ventricular ectopy or nonsustained VT. Left ventricular systolic function is an important independent predictor of mortality in these patients. Thus, patients with severe heart failure or a decreased left ventricular ejection fraction are at increased risk for sudden cardiac death.[15] Patients with evidence of myocardial ischemia (by history or exercise testing) or with a late potential on a signal-averaged electrocardiogram (ECG) after a prior MI are also at increased risk for serious or life-threatening ventricular arrhythmias.[15–21] Therefore, in assessing risk for sudden cardiac death, one should (1) obtain a thorough history, including data about the presence of organic heart disease and associated symptoms; (2) perform a complete physical examination, with particular attention to cardiac and hemodynamic status; and (3) obtain appropriate laboratory data. Laboratory data can be subdivided into noninvasive and invasive procedures.

Noninvasive laboratory procedures: The routine chest x-ray provides some useful information about chamber enlargement, valvular heart disease, and the presence of heart failure. The 12-lead ECG is mandatory and may demonstrate or suggest a number of important abnormalities, including myocardial ischemia, previous MI, ventricular aneurysm, left ventricular hypertrophy, and cardiac conduction or serum electrolyte abnormalities. Abnormalities of the PR interval, QRS complex duration and QT interval may indicate high risk for a rhythm disturbance, especially in patients taking cardioactive drugs.

A 24-hour Holter monitor should be obtained to quantify the frequency and characterize the nature of ventricular ectopy. The presence of consecutive beats and nonsustained VT should be noted. The rate, duration and morphology of nonsustained VT may also have important therapeutic implications. In addition, the Holter monitor may document overt or silent ischemia.

Left ventricular ejection fraction may be determined noninvasively by a gated blood pool scan or an echocardiogram. Although the gated blood pool scan often provides a better estimate of global left ventricular systolic function, the echocardiogram may be better for diagnosing specific cardiac abnormalities, such as valvular heart disease and hypertrophic cardiomyopathy. Left ventricular segmental wall motion abnormalities can be determined by either technique. Echo-Doppler and magnetic resonance imaging techniques can also be used to characterize underlying cardiac abnormalities.

Exercise-induced myocardial ischemia can best be demonstrated by an exercise tolerance test. Intravenous thallium-131 images are useful when repolarization abnormalities are present on the baseline 12-lead ECG or when one wishes to determine the extent of myocardium at risk for infarction. An echocardiogram obtained immediately after exercise can also accomplish this task, and may be more sensitive for ischemia than the ECG. For patients unable to exercise, dipyridamole may be administered intravenously or orally in association with thallium to demonstrate hemodynamically significant coronary artery disease.

Because abnormalities of serum potassium, calcium and magnesium may predispose to serious or life-threatening arrhythmias, serum electrolytes should be determined in nearly all patients with ventricular ectopy. Plasma levels of drugs that affect cardiac rhythm or conduction should be obtained. This is particularly important because of potential proarrhythmic effects associated with abnormally high levels of these drugs.

In certain patient groups, the signal-averaged ECG may predict those at high risk for sudden cardiac death.[17,18] This test averages between 100 and 400 heart beats, thus reducing random noise and permitting amplification and identification of low-amplitude electrical signals. Late potentials are low-amplitude electrical signals that occur at the terminal portion of the QRS complex on the signal-averaged ECG but are not apparent on the 12-lead ECG. Late potentials are associated with an increased risk for spontaneous and inducible ventricular tachyarrhythmias, particularly in patients with coronary artery disease and previous MI.[17–21] In the latter patients, the absence of late potentials on the signal-averaged ECG may be of equal or even greater value, because it indicates a low likelihood of subsequent development of a sustained ventricular tachyarrhythmia.[17–21]

Invasive laboratory procedures: Although noninvasive laboratory tests provide important anatomic and physiologic information, invasive studies are sometimes necessary to characterize further the underlying organic heart disease or ventricular arrhythmias. Indications for cardiac catheterization for patients with frequent or complex ventricular ectopy or nonsustained VT are similar to those for patients without ventricular arrhythmias. Patients thought to have significant coronary artery disease, valvular heart disease, or a cardiomyopathy that may be causing or aggravating ventricular arrhythmias should be considered for cardiac catheterization, particularly when the disease may be surgically corrected. When myocardial ischemia is strongly suspected, cardiac catheterization may be performed in place of a noninvasive evaluation.

The indications for programmed EP testing are less clear. Certainly, programmed EP testing is an accepted technique for documenting and characterizing sustained ventricular tachyarrhythmias in patients with definite or suspected tachyarrhythmias.[2] Far less is known about the use of programmed EP testing in patients who may be at increased risk for sudden cardiac death, but who have yet to demonstrate a sustained ventricular tachyarrhythmia or symptoms (such as syncope) consistent with the possible presence of a ventricular tachyarrhythmia. Furthermore, little information is available to confirm whether induction of a sustained ventricular tachyarrhythmia in these patients is predictive of subsequent, spontaneous occurrences of these arrhythmias.

It is probable that the inability to induce a sustained ventricular tachyarrhythmia in patients with coronary artery disease and a prior MI indicates a low likelihood of subsequent spontaneous development of such arrhythmias.[22–26] The ability to induce a sustained ventricular tachyarrhythmia, at the very least, suggests that the milieu to support a ventricular tachyarrhythmia is present. It is a logical, though not proven, extrapolation that spontaneous triggers (e.g., VPCs) might similarly provoke a sustained ventricular tachyarrhythmia in these patients. The available, limited data support this notion.[23–26]

Should all patients with underlying organic heart disease and frequent or complex ventricular ectopy or nonsustained VT undergo programmed EP testing during cardiac catheterization? Obviously, this is not possible, if only because of the sheer number of patients involved. Perhaps, by applying the principles of risk stratification, patients at highest risk can be identified and then considered for programmed EP testing to determine if a sustained ventricular tachyarrhythmia can be induced.

RISK STRATIFICATION TO ASSESS INDICATIONS FOR ELECTROPHYSIOLOGIC TESTING

For patients with coronary artery disease, data are accumulating that indicate that patients with a late potential on a signal-averaged ECG are at high risk for both spontaneous and inducible ventricular tachyarrhythmias.[17–21] Whether the presence of ventricular ectopy and a late potential on a signal-averaged ECG are sufficient to warrant programmed EP testing during cardiac catheterization is uncertain, although there is a growing body of evidence suggesting that this may be so.

The combination of a depressed ejection fraction (essentially $\leq$40%), frequent and complex ventricular ectopy, and a late potential on the signal-averaged ECG has been shown by Gomes et al[18] to be an important predictor of outcome. They demonstrated that each of these factors, independently, were important; that any 2, in combination, were more important; and that when a patient with a previous MI had all 3 abnormalities, the event rate of subsequent spontaneous sustained ventricular tachyarrhythmias was 50%. Data from larger studies are needed in order to weigh these risk factors with more

certainty. In terms of risk stratification, however, this constellation seems to warrant consideration for invasive EP testing, although there is no information about the inducibility of sustained VT in these patients.

That inducibility of sustained VT may be high in these aforementioned patients is suggested by studies of patients with nonsustained VT (variously described as ≥3 or ≥5 VPCs in a row at a rate of either ≥100 or ≥120 beats/min for up to 30 seconds) and coronary artery disease.[24–26] In each of these studies, there was a remarkably high incidence of inducible sustained VT (42.5, 45 and 37.5%, respectively). Besides nonsustained VT and underlying heart disease, left ventricular dysfunction appeared to be a predictor of VT in these patients.[25] One of the studies included patients with valvular heart disease, but these patients had a low incidence of inducible sustained VT. Importantly, in 2 of these studies, no subsequent spontaneous sustained VT or sudden cardiac death occurred in patients in whom sustained VT was not induced. There was an important incidence of subsequent development of spontaneous sustained ventricular tachyarrhythmia or sudden cardiac death in the patients with inducible sustained VT (25, 12 and 41%, respectively), but patients with inducible VT seemed to do best when treatment was guided by EP testing.

Because none of these 3 studies was placebo controlled, neither the incidence of proarrhythmia (clearly, a potential outcome of treatment) nor the actual incidence of spontaneous, sustained ventricular tachyarrhythmic events could be determined. Furthermore, none of these studies used electrocardiographic signal averaging, nor did they address the extent and treatment of myocardial ischemia. Nevertheless, patients who also have a late potential on the signal-averaged ECG and an abnormal left ventricular ejection fraction (in addition to nonsustained VT and coronary artery disease) may be expected to be at even higher risk for a sustained ventricular tachyarrhythmia or sudden cardiac death. Therefore, in the absence of a definitive clinical study, it seems credible to suggest, once again, that EP testing is warranted in patients with nonsustained VT, a previous MI, a late potential on the signal-averaged ECG and an ejection fraction ≤40%.

Based on available data (and recognizing that the definitive study of these patients remains to be done), if no ventricular tachyarrhythmia is induced, it is reasonable not to treat the patient unless warranted by symptoms. What then if a sustained ventricular tachyarrhythmia is sustained? Because there are no data on which to base firm recommendations, we can only suggest that a reasonable case can be made to initiate treatment.

ASSESSMENT OF THERAPY

There is a widely held belief that, in patients who present with suspected or overt VT or ventricular fibrillation, programmed EP testing is indicated not only to characterize the arrhythmia,[2] but also to guide therapy.[27] Whether quantitative serial Holter monitoring with or without exercise testing can be used in place of programmed EP testing to guide effective therapy is not yet clear. The study of Mitchell et al[28] suggests that in patients with a documented ventricular tachyarrhythmia, therapy guided by programmed EP testing is more effective than when guided by Holter monitoring, even when ventricular ectopy is sufficiently frequent to provide an end point (suppression of the ectopy). Also, as emphasized by Pratt et al,[29] many patients with life-threatening ventricular tachyarrhythmias have surprisingly little ventricular ectopy, making 24-hour ambulatory electrocardiographic monitoring as a guide for effective therapy very difficult if not impossible. However, as evidenced by the need for the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) trial (a multicenter study comparing efficacy of treatment of sustained ventricular tachyarrhythmias guided by EP testing vs quantitative 24-hour Holter monitoring)[30] and by data from other studies,[31] Holter monitoring may still be a useful guide to therapy in selected patients. When the ESVEM study is concluded, it should provide sufficient, systematically obtained data from a large enough number of patients to make a definitive statement about the value of Holter monitoring. In the meantime, available studies suggest that both techniques are useful to guide therapy in patients with documented, sustained ventricular tachyarrhythmias, although programmed EP testing provides more reliable predictors of therapeutic efficacy. However, there are some data suggesting that once VT is induced and characterized, neither EP testing nor Holter monitoring may be required to assess therapy.[32]

It is a reasonable extrapolation that the aforementioned considerations for patients with sustained VT should hold for patients who present with frequent or complex ventricular ectopy or nonsustained VT and in whom a sustained ventricular tachyarrhythmia is induced during EP testing. It is important to reemphasize that no study has shown that antiarrhythmic drug therapy improves outcome in these patients, regardless of the guidelines. Certainly, the CAST has shown that Holter monitor-guided suppression of these arrhythmias with either encainide or flecainide in patients with a recent MI results in an increased risk of sudden cardiac death, compared with a placebo-treated group.[7] Although these results may prove to be drug specific, it nevertheless indicates that suppression of ventricular ectopy and nonsustained VT in patients with a recent MI does not improve outcome as such. The data also indicate that more information is required from clinical trials before treatment recommendations can be made that are not based on speculation, reasonable though it may appear.

CONCLUSION

Clearly, patients who present with sustained VT and patients who survive ventricular fibrillation should receive antiarrhythmic therapy. Patients without underlying heart disease who have ventricular ectopy short of a sustained ventricular tachyarrhythmia should not be treated unless the symptoms are severe enough to warrant the risks of the treatment itself. A large group of patients still remain who have ventricular ectopy with or without nonsustained VT in the presence of underlying heart dis-

ease, but who have not manifested VT or ventricular fibrillation. The concern is that these patients may be at increased risk for sudden cardiac death.

Available data suggest that there are some important markers for patients with underlying heart disease (especially coronary artery disease) who are at increased risk for sudden cardiac death. These include a previous MI, myocardial ischemia, nonsustained VT, frequent or complex ventricular ectopy, abnormal ejection fraction, and the presence of a late potential on the signal-averaged ECG. Currently, there are many uncertainties about how to manage such patients. It would seem, however, that when several risk factors for sudden cardiac death are present in the same patient (namely an abnormal ejection fraction, a late potential on a signal-averaged ECG, and frequent or complex ventricular ectopy or nonsustained VT), especially after a recent MI, it is reasonable to perform an EP study to determine if a ventricular tachyarrhythmia is inducible, provided one is prepared to act on the results of the test. If no sustained ventricular tachyarrhythmia is inducible, current data suggest that the risk of subsequent, spontaneous sustained ventricular tachyarrhythmias is quite low, so that treatment is not indicated unless warranted to relieve symptoms. If a sustained ventricular tachyarrhythmia is induced, interpretation of the limited available data suggests that it is reasonable that this arrhythmia be treated. Such therapy should be guided by the same principles used to treat patients who present with sustained ventricular tachyarrhythmias. These recommendations are offered with the uncertainties that come from the absence of definitive data to guide therapy (a clinical trial with a placebo-controlled arm is sorely needed), and despite the fact that the CAST showed that suppressive treatment is not always better. Nevertheless, this group of patients with documented inducible, sustained VT at least has a known substrate for supporting a sustained ventricular tachyarrhythmia, and risk stratification parameters seem to indicate that these patients are at considerable risk.

REFERENCES

1. Surawicz B. Prognosis of ventricular arrhythmias in relation to sudden cardiac death: therapeutic implications. *JACC 1987;10:435–437.*

2. Waldo AL, Akhtar M, Brugada P, Henthorn RW, Scheinman MM, Ward DE, Wellens HJJ. The minimally appropriate electrophysiologic study for the initial assessment of patients with documented sustained monomorphic ventricular tachycardia. *JACC 1985;6:1174–1177.*

3. Prystowsky EN, Zipes DP. Electrophysiologic testing and ventricular tachycardia. In: Surawicz B, Reddy CP, Prystowsky EN, eds. Tachycardias. *Boston: Martinus Nijhoff, 1984:293–309.*

4. Kennedy HL, Whitlock JA, Sprague MK, Kennedy LJ, Buckingham TA, Goldberg RJ. Long-term follow up of a symptomatic healthy subject with frequent and complex ventricular ectopy. *N Engl J Med 1985;312:193–197.*

5. The CAPS Investigators. The Cardiac Arrhythmia Pilot Study. *Am J Cardiol 1986;57:91–95.*

6. Vlay SC. How the university cardiologist treats ventricular premature beats: a nationwide survey of 65 university medical centers. *Am Heart J 1985;110:904–912.*

7. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med 1989;321:406–412.*

8. Hoffman BF, Rosen MR, Wit AL. Electrophysiology and pharmacology of cardiac arrhythmias. III. The causes and treatment of cardiac arrhythmias. Part A. *Am Heart J 1975;89:115–122.*

9. Frazier DW, Wolf PD, Wharton JM, Tang ASL, Smith WM, Ideker RE. Stimulus-induced critical point: mechanism for the electrical initiation of reentry in normal canine myocardium. *J Clin Invest 1989;83:1039–1052.*

10. Furberg CD. Effect of antiarrhythmic drugs on mortality after myocardial infarction. *Am J Cardiol 1983;52:32C–36C.*

11. Rapaport E, Remedios P. The high risk patient after recovery from myocardial infarction: recognition and management. *JACC 1983;1:391–400.*

12. Chamberlain DA, Jewitt DE, Julian DG, Campbell RWF, Boyle DMcC, Shanks RG. Oral mexiletine in high risk patients after myocardial infarction. *Lancet 1980;2:1324–1327.*

13. IMPACT Research Group. International Mexiletine and Placebo Antiarrhythmic Coronary Trial: I. Report on arrhythmic and other findings. *JACC 1984;4:1148–1163.*

14. Elharrar B, Gaum WE, Zipes DP. Effects of drugs on conduction delay and incidence of ventricular arrhythmias induced by acute coronary occlusion in dogs. *Am J Cardiol 1977;39:544–549.*

15. Rosenthal ME, Oseran DS, Gang E, Peter T. Sudden cardiac death following acute myocardial infarction. *Am Heart J 1985;109:865–876.*

16. Ruskin JN, DiMarco JP, Garan H. Out-of-hospital cardiac arrest: electrophysiologic observation and selection of long term antiarrhythmic therapy. *N Engl J Med 1980;303:607–613.*

17. Nalos PC, Gang ES, Mandel WJ, Ladenheim ML, Lass Y, Peter T. The signal-averaged elecrocardiogram as a screening test for inducibility of sustained ventricular tachycardia in high risk patients: a prospective study. *JACC 1987;9:539–548.*

18. Gomes JA, Winters SL, Stewart D, Horowitz S, Milner M, Barreca P. A new noninvasive index to predict sustained ventricular tachycardia in sudden death in the first year after myocardial infarction: based on signal-averaged electrocardiogram, radionuclide ejection fraction and Holter monitoring. *JACC 1987;10:349–357.*

19. Kanovsky MS, Falcone RA, Dresden CA, Josephson ME, Simpson MB. Identification of patients with ventricular tachycardia after myocardial infarction: signal-averaged electrocardiogram, Holter monitoring and cardiac catheterization. *Circulation 1984;70:264–270.*

20. Denniss AR, Richards DA, Cody DV, Russell PA, Young AA, Cooper MJ, Ross DL, Uther JB. Prognostic significance of ventricular tachycardia and fibrillation induced at programmed stimulation and delayed potentials detected on the signal-averaged electrocardiograms of survivors of acute myocardial infarction. *Circulation 1986;74:731–745.*

21. Breithardt G, Borggrefe M, Haerten K. Role of programmed ventricular stimulation and noninvasive recording of ventricular late potentials for the identification of patients at risk of ventricular tachyarrhythmias after acute myocardial infarction. In: Zipes DP, Jalife J, eds. Cardiac Electrophysiology and Arrhythmias. *Orlando: Grune & Stratton, 1984:553–561.*

22. Brugada P, Green M, Abdollah H, Wellens HJJ. Significance of ventricular arrhythmias initiated by programmed ventricular stimulation: the importance of the type of ventricular arrhythmia induced and the number of premature stimuli required. *Circulation 1984;69:87–92.*

23. Richards D, Taylor A, Fahey P, Irwig S, Koo CC, Ross D, Cooper M, Kiat H, Skinner M, Uther J. Identification of patients at risk of sudden death after myocardial infarction: the continued Australian experience. In: Brugada P, Wellens HJJ, eds. Cardiac Arrhythmias: Where to Go From Here? *Mount Kisco, NY: Futura Publishing, 1987:329–341.*

24. Buxton AE, Marchlinski FE, Flores BT, Miller JM, Doherty JU, Josephson ME. Nonsustained ventricular tachycardia in patients with coronary artery disease: role of electrophysiologic study. *Circulation 1987;75:1178–1185.*

25. Klein RC, Machell C. Use of electrophysiologic testing in patients with nonsustained ventricular tachycardia: prognostic and therapeutic implications. *JACC 1989;14:155–161.*

26. Zheutlin TA, Roth H, Chua W, Steinman R, Summers C, Lesch M, Kehoe RF. Programmed electrical stimultion to determine the need for antiarrhythmic therapy in patients with complex ventricular ectopic activity. *Am Heart J 1986;111:860–867.*

27. Gottlieb C, Josephson ME. The preference of programmed stimulation-guided therapy for sustained ventricular arrhythmias. In: Brugada P, Wellens HJJ, eds. Cardiac Arrhythmias: Where to Go From Here? *Mount Kisco, NY: Futura Publishing, 1987:421–434.*

28. Mitchell LB, Duff HJ, Manyari DE, Wyse DG. A randomized clinical trial of the noninvasive and invasive approaches to drug therapy of ventricular tachycardia. *N Engl J Med 1987;317:1681–1687.*

29. Pratt CM, Thornton BC, Magro SA, Wyndham CRC. Spontaneous arrhythmia detected on ambulatory electrocardiographic recording lacks precision in predicting inducibility of ventricular tachycardia during electrophysiologic study. *JACC 1987;10:97–104.*

30. The ESVEM Investigators. The ESVEM Trial: electrophysiologic study versus electrocardiographic monitoring for selection of antiarrhythmic therapy of ventricular tachyarrhythmias. *Circulation 1989;79:1354–1360.*

31. Kim SG. The management of patients with life-threatening ventricular tachyarrhythmias: programmed stimulation or Holter monitoring (either or both)? *Circulation 1987;76:1–5.*

32. Brugada P, Lemery R, Talajic M, Della Bella P, Wellens HJJ. Treatment of patients with ventricular tachycardia or ventricular fibrillation: first lessons from the "Parallel Study." In: Brugada P, Wellens HJJ, eds. Cardiac Arrhythmias: Where to Go From Here? *Mount Kisco, NY: Futura Publishing, 1987:457–470.*

Clinical Implications of New Studies in the Treatment of Benign, Potentially Malignant and Malignant Ventricular Arrhythmias

Jeffrey L. Anderson, MD

For purposes of clinical management, ventricular arrhythmias have been divided into risk categories of benign, prognostically important (potentially malignant) and malignant. Benign arrhythmias occur in the setting of structurally normal hearts and do not require therapy unless associated with debilitating symptoms. Malignant arrhythmias such as sustained ventricular tachycardia or fibrillation deserve aggressive therapy to prevent recurrence. Arrhythmias occurring in the presence of organic heart disease (often ischemic disease) are frequently asymptomatic but prognostically important as a risk factor for sudden death or cardiac arrest. The common empiric practice to treat such arrhythmias (by about 40 to 50% of cardiologists in the United States) needs to be reassessed in the face of the Cardiac Arrhythmia Suppression Trial. For malignant arrhythmias, class IA agents (procainamide and quinidine) continue to be the standard of treatment, and class IB agents (e.g., mexiletine) may be used as alternative or additive therapy. Class IC agents are used as second-line therapy, especially in the setting of ischemic heart disease. Class III therapy with amiodarone is reserved for refractory patients because of potential toxicity. Sotalol, a new class II-III agent, may become a first-line drug. For prognostically important arrhythmias, β blockers remain the agents of choice, class IC agents are contraindicated, and class IA or IB drugs, or both, should be used conservatively (i.e., only for symptomatic arrhythmias). For symptomatic but benign arrhythmias requiring treatment, β blockers are safe although not always effective. Class IA, IB and IC agents may then be considered. In these patients, the proarrhythmic potential of quinidine and class IC agents remains a concern. Better tolerated and safer drugs are needed for symptomatic arrhythmias. Some promising class I drugs under development include moricizine, pirmenol and recainam. Treatment algorithms will evolve as new study results and new drugs become available.

(Am J Cardiol 1990;65:36B–42B)

From the University of Utah School of Medicine and LDS Hospital, Salt Lake City, Utah.

Address for reprints: Jeffrey L. Anderson, MD, Division of Cardiology, LDS Hospital, 8th Avenue & C Street, Salt Lake City, Utah 84143.

That sudden cardiac death is the most common cause of mortality in the Western World, occurring in approximately 350,000 persons per year in the United States, has been widely known in the medical community for more than a decade.[1] Electrocardiographic recordings during and shortly after collapse have shown that a ventricular tachyarrhythmia (usually, ventricular tachycardia [VT]) degenerating to ventricular fibrillation (VF) is the associated rhythm disturbance in >80% of cases.[2,3] Therapeutic approaches have included resuscitation strategies (effective in only about 20%) and identification of patients at high risk who may potentially benefit from prophylactic treatment.

Patients with a history of myocardial infarction (MI) are an important group at increased risk.[4] Ventricular arrhythmia was the first risk factor to be identified among these patients.[5,6] Studies in this decade have also shown the important contribution of left ventricular dysfunction and have confirmed an independent (two- to threefold) contribution of ventricular premature complexes (VPCs) to both arrhythmic and total cardiac death.[7–9] Reduction of this excess risk has been the objective of recent clinical trials. Although these trials have focused primarily on the testing of antiarrhythmic drugs, it is now clear that there are multiple initiating factors for sudden cardiac death, including ischemia, a metabolic or neurogenic imbalance, ventricular dysfunction and ventricular arrhythmias.[10,11] Thus, it appears likely that antiarrhythmic therapy for "prognostically important" arrhythmias, even if successful, will be only a partial solution.

CLASSIFICATION OF VENTRICULAR ARRHYTHMIAS INTO RISK CATEGORIES

Based on their specific prognostic implications, ventricular arrhythmias may be clinically classified as acute or as 1 of 3 chronic types: benign, prognostically important (or potentially malignant) and malignant (or lethal).[12,13] Risk classification depends not only on the presenting arrhythmia but also on the presence and degree of underlying cardiac disease (Table I). Treatment objectives differ by category.[14] In the benign class, arrhythmias are brought to medical attention because of associated symptoms or chance identification during evaluation for other reasons. Further assessment shows absent or minimally associated organic heart disease. Because patients with these arrhythmias generally have a favorable outcome, treatment is recommended only if there are significant, persistent, associated symptoms.[15] Malignant

TABLE I Clinical Classes of Chronic Ventricular Arrhythmias

	Arrhythmia Categories		
	Benign	Prognost. Important	Malignant
Risk of SCD	Minimal	Moderate to high	Highest
Organic heart disease	Minimal	+	+ (EF often low, <40%)
Presenting arrhythmia	VPCs, occ. Cps, rare salvos	VPCs, often Cps, salvos, VTu	Hx VTs/VF, variable chronic VPCs, Cps, VTu
Treatment objective	Reassure, relieve symptoms	Relieve symptoms, prevent SCD	Relieve symptoms, prevent recurrent VT, VF, SCD

Cps = couplets; EF = ejection fraction; Hx = history; occ. = occasional; Prognost. = prognostically; SCD = sudden cardiac death; VF = ventricular fibrillation; VPCs = ventricular premature complexes; VT = ventricular tachycardia; VTs = sustained VT; VTu = unsustained VT.

arrhythmias such as sustained VT or VF are associated with important symptoms, including presyncope, syncope or cardiac arrest. Most patients (80 to 90%) have severe organic heart disease (e.g., cardiomyopathy, valvular disease, or, most often, coronary artery disease), often with substantial left ventricular dysfunction (ejection fraction <40%). Because the recurrence rate of these arrhythmias is high (20 to 40% in the first 1 to 2 years),[1,16] aggressive prophylactic treatment is indicated unless the arrhythmias occur as the result of a transient precipitating factor, such as acute MI. Randomized, placebo-controlled trials are not available to guide treatment strategies in patients with malignant arrhythmias. However, observational studies have suggested a better prognosis in patients "responding" to their treatment regimens, as assessed by either noninvasive monitoring or electrophysiologic testing.[17–19]

Patients with prognostically important arrhythmias form an important but difficult group from a management standpoint. They represent perhaps 10 to 20% of patients seen by the general practitioner and about 50 to 60% of those coming to the attention of the cardiologist. There is agreement that management of this group should include treatment of underlying disease and that antiarrhythmic therapy should be initiated if debilitating symptoms are present (the minority). However, the use of antiarrhythmic therapy in this group for the purpose of trying to prevent sudden cardiac death is controversial.

Acute arrhythmias occur during intercurrent illness (including MI), the perioperative period, and with many acute cardiac or systemic diseases. Such arrhythmias often deserve treatment for a limited time period (until the transient factors have resolved) to prevent associated hemodynamic consequences or more malignant arrhythmias. Acute arrhythmias usually are not important in determining long-term risk, except in certain cases such as VF with anterior MI.[20]

CURRENT TREATMENT PRACTICES OF CARDIOLOGISTS IN THE U.S.A.

In 1985, Vlay[21] published a survey reporting how university cardiologists treated VPCs. Of responding cardiologists, 52 to 73% indicated they would treat asymptomatic patients with frequent or complex VPCs occurring in the convalescent phase of acute MI. We have recently surveyed a randomly selected cross section of office-, hospital- and academic-based cardiologists about their treatment attitudes.[22] There was a consensus regarding treatment for benign and malignant ventricular arrhythmias (the "end of the spectrum") but controversy about patients with potentially malignant arrhythmias (Table II). In patients with no heart disease and asymptomatic VPCs, only 1% of cardiologists routinely prescribed antiarrhythmic agents in 1988, compared with 100% who would treat patients with symptomatic sustained VT. An increasing number of cardiologists elected to prescribe therapy for patients with asymptomatic VPCs when these patients developed progressively more advanced cardiac disease, coexisting unsustained VT or associated symptoms. Subgroups in the potentially malignant group, including acute MI within 6 months or coronary artery disease with depressed ejection fraction (similar to those recruited for the Cardiac Arrhythmia Suppression Trial [CAST]), were treated by 38 to 79% of cardiologists (average 45 to 50%), even though they were asymptomatic. Beta blockers were most frequently selected as the appropriate agent for first-line therapy (80% of responses), followed by class I agents (41 to 78% response rates). Widespread use of this empiric approach to treatment emphasizes the importance of CAST results.

RESULTS AND IMPLICATIONS FROM CAST AND OTHER DRUG TRIALS

A review of early trials of class I antiarrhythmic agents in postinfarction patients does not provide support for an overall survival advantage to therapy.[23] However,

TABLE II Treatment Patterns of United States Cardiologists (1988) Before CAST

	% Cardiologists Routinely Treating Arrhythmias				
	Asymptomatic		Symptomatic		
Cardiac Status	VPC	VTu	VPC	VTu	VTs
No heart disease	1	17	66	88	100
CAD (EF >40%)	13	51	80	97	100
CAD (EF <40%)	38	76	88	98	100
AMI in <6 months	41	79	90	98	100

AMI = acute myocardial infarction; CAD = coronary artery disease; other abbreviations as in Table I.
Adapted from *Am J Cardiol.*[22]

TABLE III Effects of Encainide and Flecainide on Mortality* After Myocardial Infarction in the CAST[28]

Subgroup (No. of Pts.)	Arrhythmic Death/Cardiac Arrest Rates			Total Death/Cardiac Arrest Rates		
	Enc./Flec. (%)	Placebo (%)	Relative Risk (C.I.)	Enc./Flec. (%)	Placebo (%)	Relative Risk (C.I.)
Overall (1,455)	4.5	1.2	3.6 (1.7–8.5)	7.7	3.0	2.5 (1.6–4.5)
Selected subgroups						
Drugs (for EF ≥30%)						
Enc. or placebo (611)	4.6	1.0	4.6	6.8	2.6	2.6
Flec. or placebo (624)	2.9	0.7	4.4	5.1	2.3	2.2
Ejection fraction						
<30% (220)	9.5	3.6	2.7	17.6	6.3	2.8
≥30% (1,235)	3.7	0.8	4.5	5.9	2.4	2.4
History of prior MI						
+ (522)	9.6	1.9	5.1	15.0	3.7	4.0
0 (918)	1.9	0.9	2.1	3.8	2.7	1.4
Baseline VPCs/hour						
<50 (797)	2.6	1.5	1.7	5.4	3.2	1.7
≥50 (658)	6.8	0.9	7.2	10.3	2.8	3.7

* Average follow-up = 10 months.
C.I. = 95% confidence intervals; EF = ejection fraction; Enc. = encainide; Flec. = flecainide; MI = myocardial infarction; VPCs = ventricular premature complexes.

these studies were fraught with methodologic problems, and they yielded varying results.[24,25] Beta blockers form the only class of drugs (class II) that have consistently demonstrated the potential to reduce total mortality and, specifically, sudden death rates in patients after MI.[26] However, β blockers have many effects other than antiarrhythmic actions that may be related to their cardioprotective effects.

SUMMARY OF CAST

The most important therapeutic trials in arrhythmia patients with coronary artery disease and recent MI are the Cardiac Arrhythmia Pilot Study (CAPS) and the CAST, both supported by the National Institutes of Health.[27,28] Unexpectedly, recruitment for the encainide and flecainide arms of the ongoing CAST was discontinued in April 1989 because of an excess of arrhythmic deaths/cardiac arrests (4.5% with encainide or flecainide, 1.2% with placebo, relative risk 3.6) and total mortality/cardiac arrests (7.7% with encainide or flecainide, 3.0% with placebo, relative risk 2.5).[28] The CAST Safety Monitoring Board further recommended that the study be continued for the third drug, moricizine, which did not appear to share the same risk potential.

Hypotheses for treatment algorithms: Although clinical trials are not designed to adequately test subgroup hypotheses, subgroup analysis can generate useful hypotheses for future testing. In the CAST, an adverse therapeutic trend was consistently observed in many subgroups; however, a substantial differential risk was identified in some subgroups, including patients with a history of prior MI and those with a higher arrhythmia frequency at baseline (Table III). Among those with prior MI (about one-third of the population), the relative risk of treatment for total mortality or cardiac arrest was 4.0, and the absolute excess risk was 12.3%. In those without prior MI, the relative risk was only 1.4, and the absolute risk only 1.1%.

Possible reasons for the CAST results: The adverse therapeutic effects observed in the CAST may be attributed to either a toxic effect of a specific antiarrhythmic drug subclass (type IC) or a general class I (sodium-channel blocking) drug effect. In terms of the first possibility, class IC agents are known to have more intense, longer-acting effects than other agents.[29] Class IC agents also cause high rates of proarrhythmia in patients with malignant arrhythmias.[30,31] The recommendation of the CAST Safety Monitoring Board to continue the moricizine arm suggests that at least this drug has yet to show any adverse mortality effect compared with placebo.

The second possibility is also supported by a number of observations. Biostatisticians have emphasized that differences in degree are more likely than differences in kind when predicting the results of trials in related populations or with related treatments.[32] The fact that other antiarrhythmic trials (with drugs from class IA and IB) have not shown consistently beneficial results is noteworthy.[23] In 2 trials, e.g., mexiletine (a class IB agent with supposedly low proarrhythmic risk) showed an adverse trend on mortality,[24,33] suggesting that differences in degree rather than kind may be characteristic of effects of class I antiarrhythmic agents on postinfarction risk.

Possible mechanisms of adverse drug effect on mortality: Encainide and flecainide may have caused a higher than expected death rate in the CAST because of a high rate of their typical "proarrhythmia" or because of a separate effect, such as a facilitation of VF ("profibrillatory" effect), perhaps during transient ischemia (reduced ischemic VF threshold). Against the first explanation is the low net observed rate of drug proarrhythmia in the CAPS, in which rates with active drugs were virtually identical to rates with placebo.[27] Furthermore, the CAST was discontinued because of increases in mortality and cardiac arrest, not because of monitored proarrhythmia.

EFFECTS OF ANTIARRHYTHMIC DRUGS ON VENTRICULAR FIBRILLATION IN ANIMAL MODELS

In open-chest canine models, the cardiac threshold for VF is reduced by acute ischemia and increased by β-

TABLE IV Selected Comparisons of the Oral Antiarrhythmic Agents

		Estimated Effectiveness		Adverse Potential			
Class	Drug	B/PI* Arrhythm. (by HM)	Malignant† Arrhythm. (by PES)	Noncardiac Side Effects	Organ Toxic Potential	Proarrhythmic Risk	Negative Inotropy
IA	Quinidine	65%	25%	+++	++	++/+++	0/+
	Procainamide	60%	25%	++	++	++	+
	Disopyramide	60%	(20%)‡	++	+	++	+++
IB	Tocainide	50%	15%	++++	++	+/++	+
	Mexiletine	55%	20%	++++	+	+/++	+
IC	Flecainide	85%	25%	+	0/+	+++	++
	Encainide	80%	25%	+	0/+	+++	+/++
II	Beta blockers	50%	10%	+/++	0/+	+	++
III	Amiodarone	75%§	20%	++	++++	+	+

* Percentage of patients in whom benign (B) or prognostically important (PI) ventricular arrhythmias were reduced ≥75%, as measured by Holter monitoring (HM).
† Percentage of patients in whom malignant ventricular tachycardia was suppressed, as measured by programmed electrical stimulation (PES).
‡ Often not appropriate for patients with poor ventricular function.
§ Not approved for use in benign or potentially malignant arrhythmias.
Arrhythm. = arrhythmias; B = benign; HM = Holter monitoring; PES = programmed electrical stimulation; PI = prognostically important; 0 = no risk; + = mild risk; ++ = moderate risk; +++ = high risk; ++++ = highest risk.

blocking therapy.[34,35] A reduction in the VF threshold after acute MI also correlates with inducibility of sustained VT or VF in dogs.[35] Rates of canine VF induced by coronary ligation are also reduced (by 50%) when sympathetic nerve traffic is interrupted by sectioning of the stellate ganglion.[36] Acute ischemia plus superimposed sympathetic nerve stimulation (stellate ganglion) results in malignant ventricular arrhythmia induction in feline models.[37] In this model, Schwartz et al[37] showed that class I antiarrhythmic drugs (including mexiletine and propafenone) fail to prevent, and occasionally exacerbate, these ischemia-related arrhythmias. However, β blocker (class II), amiodarone (class III) and verapamil (class IV) therapies were effective in arrhythmia prevention.

In a more sophisticated sudden cardiac death model, fresh ischemia (via coronary thrombosis) was superimposed on old ischemic injury in a distant zone in conscious, ambulatory dogs.[38] Class II and III agents (β blockers, bretylium, amiodarone) but not class I agents (or selected calcium blockers) were effective in reducing the otherwise nearly complete (90 to 100%) mortality from VF.[39–43]

Importantly, Nattel et al[44] identified an arrhythmogenic effect of class I antiarrhythmic therapy (aprindine) in the dog when the drug was administered before coronary artery occlusion. Seventeen of 34 dogs (50%) receiving aprindine before left anterior descending (LAD) coronary artery occlusion had sustained VT or VF, compared with 5 of 34 (14%) receiving therapy after LAD occlusion ($p < 0.01$), 1 of 11 (9%) undergoing occlusion without therapy ($p < 0.05$), and 0 of 16 receiving aprindine without LAD occlusion ($p < 0.01$). Arrhythmogenic effects were ascribed to alterations in regional myocardial drug elimination after occlusion in pretreated dogs (ischemic zone concentrations averaged more than twice normal zone levels). If clinically applicable, these results suggest that adverse effects may be expected with class I antiarrhythmic agents (other than just encainide or flecainide), that treatment must be given before ischemia (coronary occlusion) to produce adverse effects (VT or VF), and that these effects may not occur during treatment in the absence of coronary occlusion.

IMPLICATIONS OF CAST FOR FUTURE ANTIARRHYTHMIC THERAPY

Therapy for arrhythmias after myocardial infarction: A clear implication of the CAST is that patients with a recent MI (<2 years) and prognostically important (although usually asymptomatic) ventricular arrhythmias should not be given therapy with encainide or flecainide. Whether other or all drugs with class I antiarrhythmic action increase risk similar to encainide is unknown. However, the adverse overall risk ratio of therapy in previous trials (most used class IA or IB drugs) appears to be lower than in the CAST (approximately 1.1).[23]

A review of available antiarrhythmic agents (Table IV) suggests that satisfactory, alternative class I therapies will not be easy to come by in these patients. In our pre-CAST survey,[22] cardiologists rated quinidine as having proarrhythmic effects comparable to encainide and flecainide, and an even higher rate of noncardiac and organ-toxic adverse effects. The adverse effects of procainamide, however, primarily relate to drug-induced lupus and, rarely, neutropenia. Disopyramide has important negative inotropic and anticholinergic effects. Thus, physicians should not assume that available drugs with class IA action will be ideal substitutes for encainide and flecainide, even in patients with symptomatic ventricular arrhythmias. Newer class IA agents, such as pirmenol, may be better tolerated.[45]

The increased mortality trends observed for treatment with mexiletine in patients after MI[24,33] and the high rate of noncardiac adverse effects with mexiletine and tocainide suggest the need for reserved judgment about the use of class IB agents. Thus, of drugs with ventricular antiarrhythmic activity, only those in class II (the β-blocking agents) currently remain.[26] Beta blockers continue to be the best choice for first-line therapy of potentially malignant arrhythmias (Table V). Because β blockers have relatively weak antiectopic effects,[14,46] the approach to patients who are unable to tolerate β-blocking therapy or

TABLE V Proposed Treatment Algorithms After CAST

Asymptomatic, prognostically important ventricular arrhythmias
Administer β-blocking therapy
Refer to CAST Study Center (moricizine)
(?)Select high-risk patients for individualized therapy and electrophysiologic study
Avoid IC agents; (?) other class I agents
Malignant arrhythmias
Class IA agents (procainamide, quinidine)
Class IB agents (mexiletine)
Class IA plus IB agents
Class IC agents
Amiodarone
Symptomatic, benign, or prognostically important ventricular arrhythmias
Beta blockers
Class IA agents (procainamide, quinidine)
Class IB agents (mexiletine)
Class IC agents (except for patients with MI and possibly other patients with CAD)

CAD = coronary artery disease; CAST = Cardiac Arrhythmia Suppression Trial; MI = myocardial infarction.

who have no relief of symptoms with it is unclear. Entry of such patients into the revised CAST study, which includes moricizine (a well-tolerated drug whose mortality effects are being carefully followed), appears to be an appealing alternative for these patients with asymptomatic arrhythmias.

Treatment of malignant arrhythmias: Before the CAST results, the known proarrhythmic effects of class IC therapy in patients with malignant arrhythmias[30,31] had led to their proposed use as second-line therapy in these patients.[46,47] After the CAST, the initial selection of class IA, class IB or combined class IA and IB agents as the initial approach (often in combination with β-blocking therapy, when appropriate) continues to be preferred (Table V), even though an increased concern about previously unsuspected adverse effects of class I agents has been raised by the CAST.

Treatment of symptomatic, benign arrhythmias: The use of class IC agents, in particular, and class I agents, in general, for treating symptomatic but prognostically benign ventricular arrhythmias is difficult to resolve. Certainly, safety concerns should reemphasize the avoidance of therapy in patients with asymptomatic or mildly symptomatic arrhythmia. In those with severe, debilitating symptoms, however, treatment is often required. Is the risk of such treatment acceptable? In the study by Nattel et al,[44] acute ischemia was a necessary prerequisite to the arrhythmogenic effects of therapy. In the CAST subgroup analysis (Table III), most of the mortality risk, both in relative and absolute terms, resided in patients with multiple MIs. Only a 1% absolute residual risk was present in those with a first MI. In patients without ischemic heart disease treated with class IC agents (and other class I agents), it appears reasonable to hope that the risk may be substantially lower than 1%. In this setting, the balance of benefit to risk may be acceptable in selected patients. For example, severe refractory angina is often treated with angioplasty or bypass surgery in subgroups in which no mortality benefit can be assured. In such selected cases, the mortality risk is justified by the symptomatic relief provided. Until more definitive data are available, a decision to treat patients with symptomatic but benign (or prognostically important) ventricular arrhythmias will require careful physician judgment. A proposed treatment algorithm for these patients is presented in Table V. Moricizine,[27] pirmenol[45] and recainam[48] are 3 antiarrhythmic agents under development that are effective and well tolerated, and may be useful additions to the available drugs that are appropriate for treatment of symptomatic ventricular (and supraventricular) arrhythmias.

Role of amiodarone: Amiodarone, a potent antiarrhythmic agent with class III action but with many potential adverse effects, is currently contraindicated for treatment of benign and potentially malignant arrhythmias, even if patients are symptomatic. With low-dose, limited term (1 to 2 years) therapy, however, its benefit-risk potential may be sufficiently favorable to warrant evaluation in selected high-risk patient groups with prognostically important arrhythmias. Cleland et al[49] evaluated clinical variables potentially predictive of mortality in 132 patients with heart failure followed for 21 months. Frequent VPCs and a diagnosis of coronary artery disease were associated with a poor prognosis. However, prognosis was improved with amiodarone therapy, which was associated with a sudden death incidence one-third that of untreated patients (15 vs 45%). The study was not randomized.

An important future arrhythmia trial with amiodarone, to be conducted by the United States Veterans Administration, is scheduled to begin in late 1989. Up to

TABLE VI Proposed Approach for Selecting and Treating Postinfarction Patients at Risk for Sudden Cardiac Death

Prevent chronic electrical instability by early thrombolytic therapy, etc.
Treat residual latent ischemia with medications, coronary angioplasty, bypass surgery
Use β blockade as general prophylactic therapy after myocardial infarction
Assess high-risk patients with combined noninvasive tests (Holter monitoring, ejection fraction measurement, signal-averaged ECG)
Perform electrophysiologic studies in highest risk subgroups
If inducible VT/VF, use drug therapy guided by electrophysiologic studies alone or combined with Holter monitoring and treadmill exercise testing

ECG = electrocardiogram; VF = ventricular fibrillation; VT = ventricular tachycardia.

TABLE VII Two-Site Model of Possible Antiarrhythmic Drug Effects on Arrhythmic Death Risk

	Patterns of Action					
Site of Action	Substrate (+)			Substrate (−)		
"Trigger" (VPCs)	↓	→	↑	↓	→	↑
"Substrate" (VFT)	↓	↓	↓	↑	↑	↑
Net effect on risk	↓↓	↓	↓, →(?↑)	↑*, →	↑	↑↑

* CAST result for class IC therapy.
CAST = Cardiac Arrhythmia Suppression Trial; VFT = ventricular fibrillation threshold; VPCs = ventricular premature complexes; (+) = substrate stabilization; (−) = substrate destabilization; ↑ = risk increased; → = risk unchanged; ↓ = risk decreased.

1,200 patients with ventricular dysfunction and arrhythmias will be enrolled in a multicenter, randomized, double-blind, parallel comparison of amiodarone and placebo. This study should help to define the benefit-risk ratio of this controversial antiarrhythmic.

Role of sotalol: Sotalol, a class III agent with additional β-blocking activity that is associated with antiarrhythmic activity greater than expected for β-blocking effect alone,[50] may be approved for general use in the near future. Sotalol has the additional advantage over many antiarrhythmic drugs of showing a beneficial mortality trend in a post-MI study.[51] However, the effect was somewhat less than that seen with other β-blocking trials.[26] In some studies, sotalol has shown particularly impressive results in preventing inducible sustained VT or VF, often in the setting of ischemic heart disease.[52] Experience with its use in the post-MI setting has not all been positive,[53] however, and its role for prophylaxis of prognostically important arrhythmias remains to be defined.

Implications of CAST for monitoring drug therapy: The CAST results suggest a need to reevaluate the methods used for assessing the risk of ventricular arrhythmias, for guiding antiarrhythmic therapy, and for establishing criteria for drug selection. In the CAST, ambulatory electrocardiographic monitoring (at least for encainide and flecainide) was prognostically misleading. Future approaches may need to incorporate signal-averaged electrocardiography[54] and electrophysiologic testing,[55–57] as suggested in Table VI.

Antifibrillatory versus antiectopic therapy: The CAST results indicate the complexity of therapeutic approaches to prevention of arrhythmic death. Treatment targets must include both the substrate and the triggering ectopy. Although it still appears possible that prognostically important VPCs are "triggering" events for malignant arrhythmias, in order to be optimally effective, therapy must have a beneficial effect on arrhythmia substrate as well as spontaneous ectopy (Table VII).[11,58]

CONCLUSION

The CAST study serves to emphasize the complexity of treatment approaches to sudden cardiac death. Our current understanding of therapy is inadequate and needs revision. New antiarrhythmic drug development is needed that will continue to provide safer, better tolerated, and more effective agents for treatment of symptomatic and, perhaps, also asymptomatic but prognostically important arrhythmias.

REFERENCES

1. Lown B. Sudden cardiac death: the major challenge confronting contemporary cardiology. *Am J Cardiol 1979;43:313–328.*

2. Kempf FC, Josephson ME. Cardiac arrest recorded on ambulatory electrocardiograms. *Am J Cardiol 1984;53:1577–1582.*

3. Pratt CM, Francis MJ, Luck JC, Wyndham CR, Miller RR, Quinones MA. Analysis of ambulatory electrocardiograms in 15 patients during spontaneous ventricular fibrillation with special reference to preceding arrhythmic events. *JACC 1983;2:789–797.*

4. Bigger JT Jr. Identification of patients at high risk for sudden cardiac death. *Am J Cardiol 1984;54:3D–8D.*

5. Ruberman W, Weinblatt AB, Goldberg JD, Frank CW, Shapiro S. Ventricular premature beats and mortality after myocardial infarction. *N Engl J Med 1977;297:750–757.*

6. Moss AJ, Davis HT, DeCamilla J, Bayer LW. Ventricular ectopic beats and their relation to sudden and non-sudden cardiac death after myocardial infarction. *Circulation 1979;60:998–1003.*

7. Bigger JT Jr, Fleiss JL, Kleiger R, Miller JP, Rolnitzky LM, and the Multicenter Post-infarction Group. The relationship between ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. *Circulation 1984;69:250–258.*

8. Mukharji J, Rude RE, Poole WK, Gustafson N, Thomas LH Jr, Strauss HW, Jaffe AS, Muller JE, Roberts R, Raabe DS Jr, Croft CH, Passamani E, Braunwald E, Willerson JT, and the MILIS Study Group. Risk factors for sudden death after acute myocardial infarction: two-year follow-up. *Am J Cardiol 1984;54:31–36.*

9. Kostis JB, Byington R, Friedman LM, Goldstein S, Furberg C. Prognostic significance of ventricular ectopic activity in survivors of acute myocardial infarction. *JACC 1987;10:231–242.*

10. Rosenthal ME, Oseran DS, Gang E, Peter T. Sudden cardiac death following acute myocardial infarction. *Am Heart J 1985;109:865–875.*

11. Anderson JL. Current clinical perspectives on antiarrhythmic drug therapy. *Fed Proc 1986;45:2213–2219.*

12. Bigger JT Jr. Definition of benign versus malignant ventricular arrhythmias: targets for treatment. *Am J Cardiol 1983;52:47C–54C.*

13. Morganroth J. Premature ventricular complexes. Diagnosis and indications for therapy. *JAMA 1984;252:673–676.*

14. Anderson JL. The new antiarrhythmic drugs: how to put them to best use. *Postgrad Med 1988;83:181–193.*

15. Kennedy HL, Whitlock JA, Sprague MK, Kennedy LJ, Buckingham TA, Goldberg RJ. Long-term follow-up of asymptomatic healthy subjects with frequent and complex ventricular ectopy. *N Engl J Med 1985;312:193–197.*

16. Cobb LA, Werner JA, Trobaugh GB. Sudden cardiac death. *Mod Concepts Cardiovasc Dis 1980;59:31–36.*

17. Graboys TB, Lown B, Podrid PJ, DeSilva R. Long-term survival of patients with malignant ventricular arrhythmia treated with antiarrhythmic drugs. *Am J Cardiol 1982;50:437–443.*

18. Swerdlow CD, Winkle RA, Mason JW. Determinants of survival in patients with ventricular tachyarrhythmias. *N Engl J Med 1983;308:1436–1442.*

19. Ruskin JN, Garan H. Electrophysiologic observations in survivors of out-of-hospital cardiac arrest related to ischemic heart disease. In Zipes DP, ed. Cardiology Clinics. *Philadelphia: WB Saunders, 1983;1:287–291.*

20. Schwartz PJ, Zaza A, Garzi S, Lombardo M, Lotto A, Skressa C, Zappa P. Effect of ventricular fibrillation complicating acute myocardial infarction on long-term prognosis: importance of the site of infarction. *Am J Cardiol 1985;56:384–389.*

21. Vlay S. How the university cardiologist treats ventricular premature beats: a nationwide survey of 65 university medical centers. *Am Heart J 1985;110:904–909.*

22. Morganroth J, Bigger JT, Anderson JL. Treatment of ventricular arrhythmias by United States cardiologists: a survey before the Cardiac Arrhythmia Suppression Trial (CAST) results were available. *Am J Cardiol 1990;65:40–48.*

23. Furberg CD. Effect of antiarrhythmic drugs on mortality after myocardial infarction. *Am J Cardiol 1983;52:32C–36C.*

24. IMPACT Research Group. International mexiletine and placebo antiarrhythmic coronary trial: I. Report on arrhythmias and other findings. *JACC 1984;4:1148–1163.*

25. Gottlieb SH, Achuff SC, Mellits ED, Gerstenblith G, Baughman KL, Becker L, Chandra NC, Henley S, Humphries JO, Heck C, Kennedy MM, Weisfeldt ML, Reid PR. Prophylactic antiarrhythmic therapy of high-risk survivors of myocardial infarction: lower mortality at 1 month but not at 1 year. *Circulation 1987;75:792–799.*

26. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta-blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis 1985;27:336–367.*

27. The Cardiac Arrhythmia Pilot Study (CAPS) Investigators. Effects of encainide, flecainide, imipramine and moricizine on ventricular arrhythmias during the first year after myocardial infarction: the CAPS. *Am J Cardiol 1988;61:501–509.*

28. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide or flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med 1989;321:406–412.*

29. Anderson JL, Bigger JT Jr, Laidlaw J, Morganroth J. Issues in the use of antiarrhythmic agents: focus on flecainide. *Pract Cardiol 1987;13:108–134.*

30. Velebit V, Podrid P, Lown B, Cohen BH, Graboys TB. Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs. *Circulation 1982;65:886–894.*

31. Morganroth J, Anderson JL, Gentzkow GD. Classification by type of ventricular arrhythmia predicts frequency of adverse cardiac events from flecainide. *JACC 1986;8:607–615.*

32. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet 1988;2:349–360.*

33. Chamberlain DA, Jewett DE, Julian DG, Campbell RWF, Boyle DMCC, Shanhs BG. Oral mexiletine in high risk patients after myocardial infarction. *Lancet 1980;2:1324–1327.*

34. Anderson JL, Rodier HE, Green LS. Comparative effects of beta-adrenergic blocking drugs on experimental ventricular fibrillation threshold. *Am J Cardiol 1983;51:1196–1202.*
35. Gang EL, Bigger JT Jr, Uhl EW. Effects of timolol and propranolol on inducible sustained ventricular tachyarrhythmias in dogs with subacute myocardial infarction. *Am J Cardiol 1984;53:275–281.*
36. Schwartz RJ, Stone HL. Left stellectomy in the prevention of ventricular fibrillation caused by acute myocardial infarction. *Circulation 1980;62:1256–1265.*
37. Schwartz PJ, Vanoli E, Zaza A, Zuanetti G. The effect of antiarrhythmic drugs on life-threatening arrhythmias induced by the interaction between acute myocardial ischemia and sympathetic hyperactivity. *Am Heart J 1985;109:937–948.*
38. Patterson E, Holland K, Eller BT, Lucchesi BR. Ventricular fibrillation resulting from ischemia at a site remote from previous myocardial infarction. A conscious canine model of sudden coronary death. *Am J Cardiol 1982;50:1414–1423.*
39. Holland K, Patterson E, Lucchesi BR. Prevention of ventricular fibrillation by bretylium in a conscious canine model of sudden coronary death. *Am Heart J 1983;105:711–716.*
40. Patterson E, Lucchesi BR. Antifibrillatory actions of d,l-nadolol in a conscious canine model of sudden coronary death. *J Cardiovasc Pharmacol 1983;5:737–744.*
41. Patterson E, Eller B, Abrams G, Vasiliades J, Lucchesi B. Ventricular fibrillation in a conscious canine model of sudden coronary death: prevention of acute and chronic amiodarone administration. *Circulation 1983;68:857–864.*
42. Lynch JJ, Coskey LA, Montgomery DG, Lucchesi BR. Prevention of ventricular fibrillation by dextrorotatory sotalol in a conscious canine model of sudden coronary death. *Am Heart J 1985;109:949–958.*
43. Kou WH, Nelson SD, Lynch JJ, Montgomery DG, DiCarlo L, Lucchesi BR. Effect of flecainide acetate on prevention of electrical induction of ventricular tachycardia and occurrence of ischemic ventricular fibrillation during the early postmyocardial infarction period: evaluation in a conscious canine model of sudden death. *JACC 1987;9:359–365.*
44. Nattel S, Pedersen DH, Zipes DP. Alterations in regional myocardial distribution and arrhythmogenic effects of aprindine produced by coronary artery occlusion in the dog. *Cardiovasc Res 1989;15:80–85.*
45. Anderson JL, Lutz JR, Nappi JM. Pirmenol for control of ventricular arrhythmias: oral dose-ranging and short-term maintenance study. *Am J Cardiol 1984;53:522–527.*
46. Morganroth J, Horowitz LN. Antiarrhythmic drug therapy 1988: For whom, how, and where? *Am J Cardiol 1989;62:461–464.*
47. Anderson JL. Criteria for selection of oral drug therapy in chronic ventricular arrhythmia. *Mod Med 1987;55(11):48–66.*
48. Anderson JL, Anastasiou-Nana MI, Heath BM, Menlove RL, Nanas JN, Friedman J. Efficacy of recainam, a new antiarrhythmic drug, for control of ventricular arrhythmias. *Am J Cardiol 1987;60:281–287.*
49. Cleland JG, Dargie HJ, Ford I. Mortality in heart failure: clinical variables of prognostic value. *Br Heart J 1987;58:572–582.*
50. Anderson JL, Askins JC, Gilbert EM, Miller RH, Keefe DL, Somberg JC, Freedman RA, Haft LR, Mason JW, Lessem JN. Multicenter trial of sotalol for suppression of frequent, complex ventricular arrhythmias: a double-blind, randomized, placebo-controlled evaluation of two doses. *JACC 1986;8:752–762.*
51. Julian DG, Prescott RJ, Jackson FS, Szekely P. Controlled trial of sotalol for one year after myocardial infarction. *Lancet 1982;1:1142–1147.*
52. Senges J, Lengfelder W, Jauernig R, Czygan E, Brachmann J, Rizos I, Cobbe S, Kubler W. Electrophysiologic testing in assessment of therapy with sotalol for sustained ventricular tachycardia. *Circulation 1984;69:577–584.*
53. Spielman SR, Kay HR, Morganroth J, Horowitz LN, Greenspan AM. Drug therapy in high risk patients following acute myocardial infarction: the results of the timolol, encainide, sotalol trial (abstr). *Circulation 1985;72:suppl III: III-15.*
54. Gomes JA, Winters SL, Stewart D, Horowitz S, Milner M, Barreca P. A new noninvasive index to predict sustained ventricular tachycardia and sudden death in the first year after myocardial infarction: based on signal-averaged electrocardiogram, radionuclide ejection fraction and Holter monitoring. *JACC 1987;10:349–357.*
55. Richards DA, Cody DV, Denniss AR, Russell PA, Young AA, Uther JB. Ventricular electrical instability: a predictor of death after myocardial infarction. *Am J Cardiol 1983;51:75–80.*
56. Mitchell LB, Duff HJ, Manyari DE, Wyse DG. A randomized clinical trial of the noninvasive and invasive approaches to drug therapy of ventricular tachycardia. *N Engl J Med 1987;317:1681–1687.*
57. Klein RC, Machell C. Use of electrophysiologic testing in patients with nonsustained ventricular tachycardia: prognostic and therapeutic implications. *JACC 1988;14:155–161.*
58. Anderson JL. Antifibrillatory versus antiectopic therapy. *Am J Cardiol 1984;54:7A–13A.*

The American Journal of Cardiology

VCM (stacks)

FEBRUARY 2, 1990

A Symposium: Thrombosis and Antithrombotic Therapy — Direction for the '90s

GUEST EDITORS:

Valentin Fuster, MD
Arthur M. and Hilda A. Master Professor
Chief, Division of Cardiology
Mount Sinai School of Medicine
New York, New York

William C. Roberts, MD
Chief, Pathology Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland
and Clinical Professor of Pathology and Medicine (Cardiology)
Georgetown University
Washington, D.C.

A YORKE MEDICAL JOURNAL/CAHNERS PUBLISHING COMPANY

Publisher's Note

The opinions expressed in this presentation are those of the panelists and are not attributable to the sponsor or the publisher, editor, or editorial board of The American Journal of Cardiology. Clinical judgment must guide each physician in weighing the benefits of treatment against the risk of toxicity. References made in the articles may indicate uses of drugs at dosages, for periods of time, and in combinations not included in the current prescribing information.

Editor's suggestion: The symposium issues for a full year should be bound together separately from the regular issues.

The American Journal of Cardiology

FEBRUARY 2, 1990 VOL. 65 NO. 6

A Symposium: Thrombosis and Antithrombotic Therapy — Direction for the '90s

GUEST EDITORS:

Valentin Fuster, MD
Arthur M. and Hilda A. Master Professor
Chief, Division of Cardiology
Mount Sinai School of Medicine
New York, New York

William C. Roberts, MD
Chief, Pathology Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland
and Clinical Professor of Pathology and Medicine (Cardiology)
Georgetown University
Washington, D.C.

This symposium was held on April 13–16, 1989, in Fort Lauderdale, Florida, and was supported by an educational grant from Du Pont Pharmaceuticals.

EDITOR IN CHIEF
William C. Roberts, MD

MANAGING EDITOR, SPECIAL PROJECTS
Judith Wagner

PUBLISHER, SPECIAL PROJECTS
Kenton T. Finch

PRODUCTION EDITOR
Vicky Weisman

PROOF EDITOR
Mary Crowell

THE AMERICAN JOURNAL OF CARDIOLOGY.® (ISSN 0002-9149) February 2, 1990, Vol. 65, No. 6 (USPS: 505–750).

Member, American Business Press, Inc. and Audit Bureau of Circulations. Published 4 times in January, February, June, July, September and October, 3 times in March, April, May, August and November, and 2 times in December, by The Cahners Publishing Company, a Division of Reed Publishing USA, 275 Washington St., Newton, MA 02158-1630. Terrence M. McDermott, President; Jerry D. Neth, Vice President/Publishing Operations; J.J. Walsh, Financial Vice President/Magazine Division; Thomas J. Dellamaria, Vice President/Production and Manufacturing.

SUBSCRIPTIONS: Solicited only from cardiologists and other physicians. Publisher reserves the right to refuse unqualified subscribers. Subscribers agree that no article or any part thereof published in any editions of the American Journal of Cardiology received under this subscription agreement may be copied, recorded or reproduced in any form or by any means, electronic or mechanical, including, among other things, photocopying or the storing of part or all of such articles on any information retrieval system, without the written permission of the Publisher. Address correspondence regarding subscriptions and changes of address to: THE AMERICAN JOURNAL OF CARDIOLOGY, 44 Cook Street, Denver, Colorado 80206-5800 (1-800-637-6073). Please include your zip code and, in case of change of address, copy of old address label. Changes of address must reach the Journal one month preceding month of issue. Single copy price: Regular issues $10.00; Symposium and special issues $12.00. Subscription rate for individuals in field of publication: United States 1 year $66, 2 years $112, 3 years $158; Canada and all other countries 1 year $105, 2 years $178, 3 years $252; Residents and Medical Students: United States 1 year $33; Canada & all other countries 1 year $85. Institutions: United States 1 year $95, 2 years $162, 3 years $228; Canada & all other countries 1 year $125, 2 years $213, 3 years $300. Air Mail available at additional charge of $150 per year. The Journal is not responsible for replacing missing issues unless the Circulation Department is notified of nonreceipt within 3 months of issue date.

Second class postage paid at Denver, CO, and at additional mailing office. Printed in U.S.A. Trademark™ in U.S. Patent Office. © Copyright 1990 by Reed Publishing USA: Saul Goldweitz, Chairman; Ronald G. Segel, President and Chief Executive Officer. All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording or by any information storage retrieval system, without permission of the copyright owner. Prices on bulk reprints of articles available on request.

The Publisher assumes no liability for any material published in the Journal. All statements are the responsibility of the authors.

MANUSCRIPTS: Address all manuscripts to William C. Roberts, MD, Editor in Chief, the American Journal of Cardiology, 7960 Old Georgetown Road, Suite 2C, Bethesda, Maryland 20814.

POSTMASTER: Send address changes to: The American Journal of Cardiology, 44 Cook Street, Denver, Colorado 80206-5800.

Cahners Publishing Company, A Division of Reed Publishing USA □ Specialized Business Magazines for Building & Construction □ Manufacturing □ Foodservice & Lodging □ Electronics & Computers □ Interior Design □ Printing □ Publishing □ Industrial Research & Technology □ Health Care □ Entertainment.

CONTENTS

The American Journal of Cardiology

FEBRUARY 2, 1990 VOL. 65 NO. 6

A SYMPOSIUM: THROMBOSIS AND ANTITHROMBOTIC THERAPY — DIRECTION FOR THE '90s

1C **Introduction** Valentin Fuster and William C. Roberts

2C **Antithrombotic Therapy in Historical Perspective** Daniel Deykin

7C **Low-Dose Warfarin and Low-Dose Aspirin in the Primary Prevention of Ischemic Heart Disease** Thomas W. Meade

12C **New Approaches to Treatment of Myocardial Infarction** James H. Chesebro, Lina Badimon, and Valentin Fuster

20C **Anticoagulant Therapy After Acute Myocardial Infarction** Alexander G.G. Turpie

24C **Thromboembolic Complications of Atrial Fibrillation and Their Prevention: A Review** Palle Petersen

29C **Valvular Heart Disease, Infected Valves and Prosthetic Heart Valves** James E. Dalen

32C **Cardiac Embolism: The Neurologist's Perspective** David G. Sherman

38C **Antithrombotic Therapy in Cardiac Disease: An Approach Based on Pathogenesis and Risk Stratification** Valentin Fuster, Bernardo Stein, Jonathan L. Halperin, and James H. Chesebro

45C **Diagnosis of Venous Thrombosis and Pulmonary Embolism** Jack Hirsh

50C **Prevention of Venous Thrombosis and Pulmonary Embolism** Vijay Kakkar

The American Journal of Cardiology

Introduction

Valentin Fuster, MD, and William C. Roberts, MD

Cardioembolic stroke is a major health-care problem in the United States. Because cardioembolic strokes tend to be massive and disabling—compared with ischemic brain infarction resulting from arterial disease—morbidity, mortality and cost of care tend to be greater.

Eighty-five percent of patients presenting with acute stroke have ischemic infarction of the brain. Of these patients with ischemic infarction, approximately 15% have their stroke as the result of a cardiac-derived embolus. An estimated $900 million is spent annually on the acute and chronic care of patients with cardioembolic stroke.

A symposium held in April, 1989, under the sponsorship of the Georgetown University School of Medicine, addressed the challenge of cardioembolic stroke. Entitled *Thrombosis and Antithrombic Therapy: Direction for the '90s*, the symposium was a forum for international specialists in thromboembolic disease. In 2 days of presentations and workshop sessions, clinicians and researchers presented the latest thinking on the prevention and treatment of thrombotic disorders from the perspectives of the cardiologist, neurologist and surgeon.

Emphasis was placed on chronic atrial fibrillation, which is the most common cause of cardiogenic stroke (in the absence of rheumatic heart disease) and accounts for 75,000 strokes annually. Symposium attendees heard the results of the recent Copenhagen Atrial Fibrillation Aspirin-Anticoagulation (AFASAK) study of the effects of anticoagulation therapy in the prevention of thromboembolic events in patients with chronic nonrheumatic atrial fibrillation.

The symposium examined therapeutic strategies for strokes related to emboli after acute myocardial infarction. Evidence was presented that administering aspirin or anticoagulant therapy in patients who have had a myocardial infarction is associated with several potential benefits.

The major causes of systemic embolism from valvular heart disease and prosthetic and infected valves were also reviewed . The Second American College of Chest Physicians Conference on Antithrombotic Therapy recently issued recommendations for therapy with anticoagulants. Several of these recommendations were discussed at this symposium, including those pertaining to the clinical effectiveness and improved safety of less intense warfarin therapy.

The management of thrombosis links the clinician with the work of clinical and basic-science researchers. We hope that the information contained in these proceedings will assist clinicians in providing safe and effective antithrombotic therapy for their patients.



***Left*, Valentin Fuster, MD; *right*, William C. Roberts, MD**

Antithrombotic Therapy in Historical Perspective

Daniel Deykin, MD

The history of antithrombotic therapy is traced over the past 5 decades, with a focus on the treatment of 2 major disorders: venous thromboembolism and acute myocardial infarction. Five subjects pertinent to clinical management decisions are discussed: (1) theories of thrombosis and coagulation, (2) tests of coagulation, (3) the availability of therapeutic interventions, (4) techniques for the diagnosis of vascular obstruction, and (5) the use and misuse of clinical trials.

(Am J Cardiol 1990;65:2C–6C)

From Boston Veterans Administration Medical Center, Boston, Massachusetts. This study was supported in part by the Medical Research Service, Veterans Administration, Boston, Massachusetts.

Address for reprints: Daniel Deykin, MD, 151-I Boston Veterans Administration Medical Center, 150 South Huntington Avenue, Boston, Massachusetts 02130.

This review of the history of antithrombotic therapy over the past 5 decades will focus on the treatment of 2 major disorders: venous thromboembolism and acute myocardial infarction (MI). Specific attention will be given to the influence on clinical decision-making of 5 elements: (1) theories of thrombosis and coagulation, (2) tests of coagulation, (3) the availability of therapeutic interventions, (4) techniques for the diagnosis of vascular obstruction, and (5) the use and misuse of clinical trials.

SETTING THE STAGE: 1940

In 1940, knowledge of the coagulation mechanism was extremely crude. At the turn of the century, Morawitz[1] had assembled existing knowledge of coagulation into a workable scheme that included fibrinogen, prothrombin, calcium, and a postulated thrombokinase or thromboplastin that converted prothrombin to thrombin. In the subsequent 40 years, however, little progress was made, except for the isolation of antihemophilic globulin in 1937.[2] The respective roles of platelets, antihemophilic globulin and surface activation were undefined. Virchow[3] had elaborated his famous triad almost 90 years previously, but there was still no understanding of how stasis, local vascular injury, and systemic changes in coagulability of blood caused thrombosis. No workable theories were at hand to distinguish between the development of arterial thrombosis and venous thrombosis, although their gross and microscopic morphologic characteristics were clearly distinct.

Antithrombotic therapy was at the threshold of widespread clinical application. Heparin had been isolated and its large-scale manufacture accomplished.[4] Similarly, in 1939 dicumarol was identified as the agent in spoiled sweet clover that caused hemorrhage in cattle.[5] Its manufacture, too, had been implemented. Within months it was introduced into clinical practice.

Theories of blood clotting were relatively simplistic, judged by our current perspective, but tests of coagulation that could be used to monitor anticoagulant therapy had already been introduced and standardized. The prothrombin time test had been developed by Quick.[6] It was used to investigate the bleeding disorder in cattle, which led to the discovery of dicumarol; it was later used to monitor dicumarol therapy when such therapy was first instituted at the Mayo Clinic.

An alternative test to monitor dicumarol therapy, the Russell's viper venom test, was used briefly by Dr. Irving Wright when he first began using dicumarol; he soon observed that this test was not useful, because frank bleeding developed in most patients monitored with the test.[7] In retrospect, we know that since the test is insensitive to factor VII, its lack of utility was not surprising. Similarly, the whole blood clotting time, widely recog-

nized to be imprecise at best, was accepted, although grudgingly, as the best available monitor for heparin therapy.

Diagnostic tests for the presence of thrombosis were also relatively unsophisticated. The electrocardiogram could define a transmural MI, and the chest x-ray could validate the presence of substantial pulmonary infarction. However, lesser or intermediate stages of occlusion in either the venous or coronary circulation, even though known clinically, were difficult to diagnose. Venography had been introduced by 1940,[8] but because the technique was not standardized, it rapidly fell from favor.

Finally, we need to reflect on the state of clinical trials in medicine in 1940. Although the concept of randomization of patients to placebo or drug therapy had been used in 1931,[9] the widespread use of large clinical trials lay in the future. None had been attempted up to 1940, and the method was not yet developed. It is appropriate to pay tribute to the wisdom of Dr. Charles Best, who wrote in 1938, "If the clinical investigation of cardiac cases should be initiated, the necessity for studying very large numbers and of heparinizing only alternate cases is obvious." [10]

Thus, the era of antithrombotic therapy was launched in 1940, with little theoretical knowledge and with crude methodology, but with 2 good drugs and 2 good tests. What has remained remarkable over these 50 years since 1940, is how successful the therapy has been, and—until very recently—how little our rapidly increasing knowledge of theory has contributed to that success.

DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM

The history of antithrombotic treatment for deep venous thrombosis and pulmonary embolism can be divided conveniently into 2 equal parts—the first, from 1940 to 1964, and the second, from 1964 to the present. The dividing point is marked neither by striking changes in theories of clotting or thrombosis nor by changes in therapy. The trial of Baritt and Jordan in 1960[11] had definitively established the effectiveness of heparin and oral anticoagulants in the prevention of recurrent pulmonary embolism, but large-scale trials of prophylaxis were still to come. What marked the division of the 2 periods was the introduction of new techniques for the diagnosis of pulmonary embolism.

The first period, from 1940 to 1964, was characterized by rapid acceptance of antithrombotic therapy, even in the absence of convincing clinical studies to support that acceptance. After the synthesis of heparin, it was introduced with impressive speed into the clinical management of patients with established deep venous thrombosis. By 1940, more than 1,000 patients had been treated. In 1941, three groups—Meyer and his associates at the University of Wisconsin, Allen and his group at the Mayo Clinic, and Irving Wright in New York—all reported successful administration of dicumarol to patients with thrombophlebitis. In 1942, the 3 groups presented their data jointly before the American Society of Clinical Investigation, and the sequential use of heparin followed by dicumarol became the standard of therapy[7] within 3 years of their introduction—an impressive feat. In contrast, despite an explosive development of knowledge of the blood clotting system over the next 20 years, there were no major advances in the treatment of deep venous thrombosis, with 1 exception—the introduction of warfarin in the early 1950s.[4] The water-soluble coumarin rapidly proved superior to dicumarol, and by 1960 warfarin had become the standard oral agent to supplement heparin in the treatment of deep venous thromboembolic disease.

How good was this treatment? In 1958, Wessler and I reviewed the then current theory and practice.[12] We wrote "... problems in diagnosis ... demonstrate how difficult it is to record the true incidence of venous thrombosis—knowledge of which is so crucial for the evaluation of therapy .... Venous thrombosis represents a common, frequently systemic disease, manifest clinically by local intravascular coagulation. The specific etiology is unknown, the diagnostic criteria are crude and unsatisfactory, and although the clinical course is unusually benign and self-limited, it may be unpredictably recurrent and lethal. It is extremely difficult at present to validate statistically any therapeutic measure; this problem will not be significantly altered until an accurate test for thrombosis is devised."

That assessment stood for another 8 years. The crucial exception was the pivotal trial by Baritt and Jordan[11] that demonstrated unequivocally the effectiveness of heparin followed by an oral coumarin derivative in the prevention of recurrent pulmonary embolism. Although the trial was imperfect by today's standards, it was so conclusive that it has never been challenged, nor should it be.

A dramatic change took place in the years following 1964. In short order, pulmonary angiography and lung scanning with macroaggregated albumin were introduced, and the diagnosis of pulmonary embolism, which had been elusive, now became definitive.[13–15] Within a few years ^{125}I fibrinogen leg scanning[16] had been developed, and venography[17] was reintroduced and standardized as the putative gold standard for the diagnosis of deep venous thrombosis. Impedance plethysmography[18] followed.

These tests set the stage for a series of trials that have taken us from uncertainty to relative certainty in the diagnosis of venous thromboembolism, and from a treatment philosophy that was reactive to one that is increasingly proactive. Furthermore, and at long last, theory contributed to practice. With the knowledge of how heparin acted, through its allosteric alteration of antithrombin III, came the theoretical development of 2 mutually distinct forms of therapy: One, low-dose subcutaneous heparin, could be used prospectively to prevent the initial bout of deep venous thrombosis in persons who were at risk. The other, full-dose heparin followed by oral anticoagulants, was to be used as treatment for patients in whom frank thrombosis had developed, which could now be accurately diagnosed.[19]

Just as the trial by Baritt and Jordan established the effectiveness of full-dose heparin and oral anticoagulants in the treatment of pulmonary embolism, so did the inter-

national multicenter large-scale trial of low-dose heparin establish the benefit of treating those postoperative patients at risk.[20] Despite initial reservations, low-dose heparin has stood the test of time, as reflected in the recent overview by Collins et al.[21]

The availability of definitive means of diagnosis of deep venous thrombosis and pulmonary embolism established diagnostic precision, and permitted us to refine treatment regimens to facilitate maximal therapeutic gain while minimizing hemorrhagic risk.[22–24]

A critical reader may wonder where fibrinolytic therapy is in this review. Unlike heparin and warfarin, fibrinolytic therapy remains a therapeutic sideshow in the treatment of venous thrombosis. The landmark urokinase-heparin pulmonary embolism trial[25] demonstrated that there was more rapid resolution of pulmonary embolism with urokinase plus heparin than with heparin alone, but the trial showed no major clinical benefit from that accelerated lysis. In particular, since this trial was not designed to show differences in mortality, it could not prove that the additional cost and hemorrhagic risk were worthwhile. Similarly, many small studies have shown that fibrinolytic agents in addition to heparin accelerate the lysis of peripheral venous thrombi, but the benefit remains uncertain.[26]

What, then, are the unresolved issues and prospects for the next decade in the diagnosis and treatment of deep venous thrombosis? First, we need to develop a fundamental understanding of the pathogenesis of deep venous disease, so that we may design better drugs and ultimately eliminate the disease itself. There is a pressing urgency to develop and standardize tests for the antithrombotic rather than anticoagulant actions of heparin and warfarin. The activated partial thromboplastin time and prothrombin time tests were designed for the diagnosis of hemorrhagic disorders. They have been used in the treatment of thrombotic disorders to ward off bleeding, but they do not address the antithrombotic potential of heparin and warfarin. The new prothrombin fragment 1-2 test developed by Bauer and Rosenberg[27] holds great promise, but it needs to be validated in large-scale clinical trials.

We should develop better noninvasive techniques for the diagnosis of deep venous thrombotic disease. Impedance plethysmography is awkward. Ultrasound holds promise,[28] but must be refined. Finally, clinical trials are needed to establish the optimal range of warfarin therapy—defined not only by tests of clotting, but most important, by tests of antithrombotic effectiveness. We should settle the question of the proper role of fibrinolytic agents in the treatment of venous thromboembolism.

ACUTE MYOCARDIAL INFARCTION

It is appropriate to begin a discussion of the antithrombotic treatment of acute MI by quoting from Charles Best's 1940 lecture to the Harvey Society: "Heparin has been used in a few cases of coronary thrombosis in human beings, but not in a scientific manner . . . Judging from experimental work, the incidence of mural thrombosis and the extension of coronary thrombi, if this occurs, would be inhibited . . . Since [heparin] is the only material available which prevents the growth of thrombi . . . the clinical cardiologist might explore its possibilities in a carefully controlled series of observations. He will of course have no preconceived ideas with regard to its therapeutic value in the condition which he is studying, but he may start his investigation with the knowledge that if [heparin is] given in adequate amounts, further thrombus formation will be prevented. He will also have to bear in mind that heparin, like many other effective weapons, is a two-edged sword, and that its function is to prevent coagulation as well as to inhibit thrombus formulation." [29]

Dr. Irving Wright was the first clinical cardiologist to test anticoagulant treatment of acute MI. On the basis of preliminary data Wright et al[30] had accumulated during World War II, the American Heart Association in 1946 initiated the first large-scale prospective trial of heparin and dicumarol in acute MI. Data were collected from 16 hospitals, on 800 patients; 368 of them, admitted on even days, received conventional therapy and constituted a control group; 432, admitted on odd days, received heparin followed by dicumarol for a minimum of 30 days.

The results were spectacular: Twenty-four percent of the control patients died; 15% of the treated patients died. Thromboembolic complications occurred in 36% of control and in 14% of treated patients. In those control patients who did not have thromboembolism, death occurred in 14%. In the treated group, the death rate among those who did not have thromboembolism was 12%, an insignificant difference. Thus, Wright's study showed that heparin and dicumarol reduced thromboembolism dramatically, and it was this action of the drugs that reduced overall mortality.

On the basis of these data, the American Heart Association made 2 recommendations in 1948, just 2 years after beginning the study:

1. Anticoagulant therapy should be used in all cases of coronary thrombosis with MI, unless a definite contraindication exists.

2. In the absence of other hemorrhagic states, the hazards from hemorrhage due to anticoagulants are not sufficient to contraindicate their use in the treatment of coronary occlusion, provided there are facilities for adequate clinical control.[30]

Thus began the era of anticoagulant therapy for MI. Despite Best's caution, the potential weaknesses of Wright's study were overlooked, and an era of uncritical enthusiasm ensued. As time progressed and studies proliferated, the apparent magnitude of benefit of anticoagulants waned and skepticism mounted, culminating in a critical broadside by Feinstein in 1969.[31] He examined 32 studies of the use of anticoagulants in acute MI, and compared their conclusions with their methodologic quality. He found that "anticoagulant therapy was ranked superior to none more often in reports that failed to fulfill . . . methodologic standards than in reports that did." In short, good outcome was associated with sloppy science.

The subsequent publication of 3 excellent randomized trials[32–34] that favored the use of anticoagulants prompted Chalmers et al,[35] in 1977, to conclude that in fact the

data did support their use in acute MI. They stated that, "All patients who present no specific contraindication should receive anticoagulants during hospitalization for infarction." However, the battle was lost, and anticoagulant therapy for MI has continued to this day to be in disfavor.[36,37]

The focus on mortality overshadowed the real gain of anticoagulant therapy: suppression of cardiogenic embolization to the brain, an unequivocal benefit achieved at minimal risk.[38] The issue needs to be reexamined, but as we shall see, in a new setting.

While the controversy raged over anticoagulants in MI, 2 developments were making the battle progressively irrelevant. The first was the flowering of research into platelet function, biochemistry and pathophysiology. It began with the discovery of adenosine diphosphate as the endogenous substance that promoted platelet aggregation, and was followed by recognition of the roles of thromboxane and prostacyclin as modulators of platelet and vascular participation in hemostasis. After that came recognition of the role of a releasable platelet moiety—platelet-derived growth factor—that linked hemostasis to atherosclerosis. New theories of thrombosis emerged that shifted the emphasis away from coronary thrombosis due to blood clotting as the primary cause of MI, to a major emphasis on platelets as the primary agents, with blood clotting as a secondary event.[39,40]

Since aspirin had been shown to impair thromboxane formation, a new era of clinical trials was initiated, testing aspirin first for its effectiveness in preventing recurrent MI, and more recently for its effectiveness in preventing the initial infarction itself. Furthermore, after the introduction and widespread use of coronary artery bypass graft surgery, recognition of the role of platelets in graft occlusion prompted a series of studies of aspirin's ability to maintain graft patency. The results have shown that, overall, aspirin provides a modest benefit in preventing graft occlusion, a probable but not certain benefit in reducing the rate of reinfarction, and a less certain benefit as a primary preventive agent.[41–43] Because full-dose warfarin and higher doses of aspirin are an incompatible mixture, aspirin has supplanted warfarin, but the evidence favoring aspirin remains less than overwhelming.

Just as aspirin began to achieve predominance as the major therapeutic agent in the treatment of MI, the emergence of interventional cardiology led to an ironic development that was to reemphasize the role of blood coagulation in acute MI. When DeWood et al[44] performed coronary angiography in patients with acute MI and demonstrated that 90% of infarct-related vessels were occluded with a fresh thrombus, they summoned fibrinolytic therapy to center stage from the wings, where it had languished as a therapy for venous thrombosis.

The past decade has witnessed the rapid evolution of an impressive array of fibrin-specific fibrinolytic agents and the rediscovery of the use of the oldest agent, streptokinase. The recent Gruppo Italiano per lo Studio della Streptokinase nell' Infarcto Miocardico (GISSI-1),[45] Anglo-Scandinavian Study of Early Thrombolysis (ASSET)[46] and Secondary International Study of Infarct Survival (ISIS-2)[47] trials have unequivocally demonstrated that administration of fibrinolytic agents early in the course of an evolving MI reduces in-hospital mortality. The ISIS-2 trial established that the combination of aspirin and a fibrinolytic agent reduces acute mortality by as much as 40%. This astonishing outcome is so dramatic that any new therapeutic regimen must offer at least as much benefit to be considered ethical.

A new generation of trials now underway will test the newer types of fibrinolytic agents against streptokinase. Whether any agent emerges that will prove to be more cost-effective than streptokinase itself remains to be seen. What is abundantly clear is that we have entered a new era of large trials, enrolling many thousands of patients on a scale not envisioned even a decade ago. Even though these trials are formidably expensive, they have answered questions that we needed to have answered, but were unable to ask.

This brief review has considered the trials and tribulations of antithrombotic therapy over the past half century. Given the rapid rate of change in medical research over the past decade it would be presumptuous, indeed, to peer too far into the future. However, I should like to set out a few short-term goals that may be attained.

The first one is to define more accurately the population at risk for arterial thrombosis and to study the effectiveness in that population of existing antithrombotic modes of therapy, singly and in combination. We also need new techniques for noninvasive diagnosis of arterial occlusion, to allow better definition of intermediate outcomes in clinical trials of drug effectiveness.

We need to explore the potential benefit of combinations of lower doses of anticoagulants and antiplatelet agents used together which might be more beneficial and safer than either agent used alone. Two candidate populations for such trials come immediately to mind: the postmyocardial infarction patient, to reduce the risk of both cerebral embolism and recurrent infarction; and the postangioplasty patient, to achieve and maintain higher patency rates than we are now obtaining.

We need better antiplatelet agents than aspirin. On the horizon is a new class of drugs that will interfere with platelet adhesion to injured vessels, the critical first step in platelet-mediated thrombosis.

The vista for new strategies in antithrombotic therapy is expanding. It is heartening, however, to reflect on the substantial advances we have already achieved. It has been a personal privilege to have taken part for the past 30 years in the development of antithrombotic therapy, and I look forward with great anticipation to new developments yet to come.

REFERENCES

1. Morawitz P. Die Chiemie der Blutgerinnung. *Ergebnisse der Physiologie biologischen Chemie und Experimental Pharmakologie 1905;4:307–422.*

2. Patek AJ Jr, Taylor FHL. Hemophilia II. Some properties of a substance obtained from normal plasma, effective in the clotting of hemophilic blood. *J Clin Invest 1937;16:113–124.*

3. Virchow R. Gesammelte Abhandlungen zur wissenschaftlichen Medicin. *Frankfurt: Meidinger Sohn, 1856:219.*

4. Best CH. Preparation of heparin and its use in the first clinical cases. *Circulation 1959;19:79–86.*

5. Link KP. The discovery of dicumarol and its sequels. *Circulation 1959;19:97–*

107.

6. Quick AJ. The development and use of the prothrombin tests. *Circulation 1959;19:92–96.*

7. Wright IS. Experience with anticoagulants. *Circulation 1959;19:110–113.*

8. Dougherty J, Homans J. Venography, a clinical study. *Surg Gynecol Obstet 1940;71:697–702.*

9. Amberson JB Jr, McMahon BT, Pinner M. A clinical trial of sanocrysin in pulmonary tuberculosis. *Am Rev Tuberculosis 1931;24:401–435.*

10. Solandt DY, Best CH. Heparin and coronary thrombosis in experimental animals. *Lancet 1938;2:130–132.*

11. Baritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. *Lancet 1960;1:1309–1312.*

12. Wessler S, Deykin D. Theory and practice in acute venous thrombosis. *Circulation 1958;18:1190–1214.*

13. Sasahara AA, Stein M, Simon M. Pulmonary angiography in the diagnosis of thromboembolic disease. *N Engl J Med 1964;270:1075–1081.*

14. Wagner HN Jr, Sabitson DC Jr, Iio M. Diagnosis of massive pulmonary embolism in man by radioisotope scanning. *N Engl J Med 1964;271:377–384.*

15. Wagner HN Jr, Tow DE. Radioisotope scanning in the study of pulmonary circulation. *Prog Cardiovasc Dis 1967;9:382–384.*

16. Flanc C, Kakkar VV, Clarke MD. The detection of venous thrombosis of the leg using ^{125}I-labelled fibrinogen. *Br J Surg 1968;55:742–747.*

17. Rabinov K, Paulin S. Roentgen diagnosis of venous thrombosis in the leg. *Arch Surg 1972;104:134–144.*

18. Hull R, van Aken WG, Hirsh J, Gallus AS, Hoichka G, Turpie AGG, Walker I, Gent M. Impedance plethysmography using the occlusive cuff technique in the diagnosis of venous thrombosis. *Circulation 1976;53:696–700.*

19. Deykin D. Current status of anticoagulant therapy. *Am J Med 1982;72:659–664.*

20. International Multicentre Trial. Prevention of fatal postoperative pulmonary embolism by low doses of heparin. *Lancet 1975;2:45–51.*

21. Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. *N Engl J Med 1988;318:1162–1173.*

22. Salzman EW, Deykin D, Shaprio RM, Rosenberg R. Management of heparin therapy: controlled prospective trial. *N Engl J Med 1975;292:133–135.*

23. Hirsh J, Poller L, Deykin D, Levine M, Dalen JE. Optimal therapeutic range for oral anticoagulants. *Chest 1989;95:suppl:5S–11S.*

24. Hyers TM, Hull RD, Weg JG. Antithrombotic therapy for venous thromboembolic disease. *Chest 1989;95:suppl:37S–51S.*

25. Kakkar VV, Lawrence D. Hemodynamic and clinical assessment after therapy of acute deep vein thrombosis. *Am J Surg 1985;10:54–63.*

26. The Urokinase Pulmonary Embolism Trial. A national cooperative study. *Circulation 1973;47:suppl:1–100.*

27. Bauer KA, Rosenberg RD. The pathophysiology of the prethrombotic state in humans: insights gained from studies using markers of hemostatic system activation. *Blood 1987;70:343–350.*

28. Lensing AWA, Prandoni P, Brandjes D, Huisman PM, Vigo M, Tomasella G, Krekt J, Wouter Ten Cute J, Huisman MV, Buller HR. Detection of deep-vein thrombosis by real-time B-mode ultrasonography. *N Engl J Med 1989;320:342–345.*

29. Best CH. Heparin and thrombosis. *Harvey Lecture Series 1940–1941;36:66–90.*

30. Wright IS, Marple CD, Bech DF. Report of the committee for the evaluation of anticoagulants in the treatment of coronary thrombosis with myocardial infarction. *Am Heart J 1948;36:801–815.*

31. Gifford RG, Feinstein AR. A critique of methodology in studies of anticoagulant therapy for acute myocardial infarction. *N Engl J Med 1969;280:351–357.*

32. Assessment of short-term anticoagulant administration after cardiac infarction: report of the Working Party on Anticoagulant Therapy in Coronary Thrombosis to the Medical Research Council. *Br Med J 1969;1:335–342.*

33. Drapkin A, Merskey C. Anticoagulant therapy after acute myocardial infarction: Relation of therapeutic effect to patient's age, sex, and severity of infarction. *JAMA 1972;222:541–548.*

34. Participants in the Veterans Administration Cooperative Study. Anticoagulants in acute myocardial infarction: results of a cooperative clinical trial. *JAMA 1973;225:724–729.*

35. Chalmers TC, Matta RJ, Smith H Jr, Kunzler AM. Evidence favoring the use of anticoagulants in the hospital phase of acute myocardial infarction. *N Engl J Med 1977;297:1091–1096.*

36. Mitchell JRA. Anticoagulants in coronary heart disease—retrospect and prospect. *Lancet 1981;1:257–262.*

37. Dalen JE, Goldberg RJ, Gore JM, Struckus J. Therapeutic interventions in acute myocardial infarction. *Chest 1984;86:257–262.*

38. Deykin D. Anticoagulants in acute myocardial infarction. In: Wessler S, Becker CG, Nemerson Y, eds. New Dimensions in Warfarin Prophylaxis. *New York: Plenum, 1987:231–241.*

39. Maseri A, Chierchia S, Davies G. Pathophysiology of coronary occlusion in acute infarction. *Circulation 1986;73:233–239.*

40. Williams LT. Signal transduction by the platelet-derived growth factor. *Science 1989;243:1564–1570.*

41. Antiplatelet Trialists' Collaboration. Secondary prevention of vascular disease by prolonged antiplatelet treatment. *Br Med J 1988;296:320–331.*

42. The Steering Committee of the Physicians' Health Study Research Group Special report: preliminary report: findings from the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med 1988;318:262–264.*

43. Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K, Warlow C, Hafner B, Thompson E, Norton S. Randomized trial of prophylactic daily aspirin in British male doctors. *Br Med J 1988;296:313–316.*

44. DeWood MA, Spores J, Notske R, Mouser LT, Burroughs R, Golden MS, Lang HT. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med 1980;303:897–902.*

45. Gruppo Italiano per lo Studio della Streptokinase nell' Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic therapy in acute myocardial infarction. *Lancet 1986;1:397–402.*

46. Wilcox RG, Von der Lippe G, Olsson CG, Jensen G, Skene AM, Hampton JR. Trial of tissue plasminogen activator for mortality in acute myocardial infarction: Anglo-Scandinavian Study of Early Thrombolysis (ASSET). *Lancet 1988;2:525–530.*

47. ISIS-2 (Secondary International Study of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both or neither, among 17,187 cases of suspected acute myocardial infarction. *Lancet 1988;2:346–360.*

Low-Dose Warfarin and Low-Dose Aspirin in the Primary Prevention of Ischemic Heart Disease

Thomas W. Meade, DM

The thrombotic component in ischemic heart disease (IHD) is now universally recognized. It is therefore logical to consider modifying both fibrin formation and platelet function in primary (as well as secondary) prevention. The scientific case for evaluating lower-dose warfarin in primary prevention rests on the implications of the secondary prevention trials, increasing evidence of an association between the level of factor VII coagulant activity, VII_c, and the incidence of IHD, and the results of short-term lower-dose trials for the prevention of venous thrombosis and thromboembolism. The general case for considering aspirin in primary prevention is well known, but the potential value of low-dose aspirin in men at high risk needs to be established. Currently available evidence suggests that the combination of lower doses of both warfarin and aspirin in primary prevention may be effective and safe. The objective of the factorial Thrombosis Prevention Trial is to demonstrate a reduction in the incidence of IHD in men at high risk attributable to low-dose warfarin or low-dose aspirin, or both, with 1 group receiving both active treatments. The feasibility of this trial has been demonstrated. An International Normalized Ratio of about 1.5, achieved with an average daily dose of 4.6 mg warfarin, has resulted in no increase in the number of men ever reporting minor bleeding episodes, although rectal bleeding occurs more frequently in those men who do report this symptom.

(Am J Cardiol 1990;65:7C–11C)

Although disputed until comparatively recently, a thrombotic component in ischemic heart disease (IHD) is now almost universally recognized. Pathologic and clinical evidence has demonstrated the thrombotic contribution not only to myocardial infarction (MI), but also to unstable angina pectoris and sudden coronary death.

An obvious point—although infrequently acknowledged—is the varying composition of thrombi at different sites. Venous thrombi are largely composed of fibrin and red cells. Coronary artery thrombi may vary from predominantly platelet bodies in the vessel wall to mainly fibrin accumulations in the lumen. It is possible that platelets are chiefly responsible for the thrombotic component of unstable angina. The obvious value of oral anticoagulants in preventing venous thrombosis, and the possibility (although by no means the certainty) that aspirin is particularly valuable in patients with unstable angina are perhaps clinical reflections of these pathologic distinctions. Especially in MI and sudden coronary death, where both platelet aggregates and fibrin deposition may be involved, it seems logical to consider modifying both in attempts at primary prevention. However, it is also worth bearing in mind the influence of the coagulation system on platelets. Thrombin (Fig. 1) is a potent platelet-aggregating agent as well as being responsible for the conversion of fibrinogen to fibrin. Furthermore, thrombin-induced aggregation is not inhibited by aspirin, and it may therefore be a pathologically significant mechanism even in patients taking aspirin prophylactically. If so, there is added reason for trying to limit the potential for thrombin production in people at high risk.

Finally, thrombosis may contribute to the onset of clinically manifest IHD not only as an acute complication of atheroma and plaque rupture, but also as a result of the chronic process of atherogenesis.

WARFARIN

Until very recently, the proposition that even in lower doses warfarin might be used in the primary prevention of IHD would have been dismissed out of hand. However, the scientific case for this approach is strong, and it rests on evidence from several different sources (Table I).

First, oral anticoagulants reduce mortality after MI by about 20%.[1,2] However, many deaths soon after infarction are electrical in origin, and are therefore not amenable to prevention by antithrombotic agents. Confining attention to events that are almost entirely thrombotic in origin—such as recurrent MI and thromboembolism—shows that oral anticoagulants reduce episode rates by about 50%.[3,4] In short, they are extremely effective in these circumstances.

From Northwick Park Hospital, Harrow, England.

Address for reprints: Thomas W. Meade, DM, MRC Epidemiology and Medical Care Unit, Northwick Park Hospital, Harrow HA1 3UJ, England.

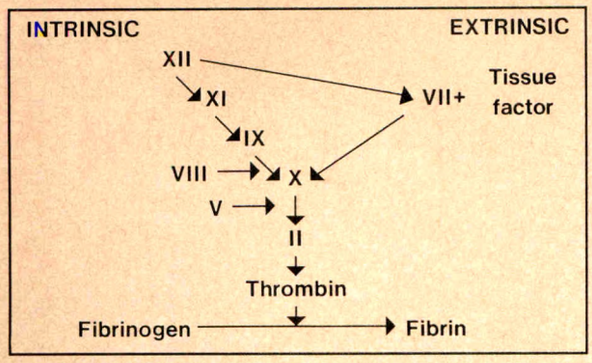


FIGURE 1. A summary of the coagulation cascade.

TABLE I Lower Dose Warfarin in the Primary Prevention of Ischemic Heart Disease

Implications of secondary prevention trials
VII_c and risk of ischemic heart disease
VII_c and thrombin production
Short-term low-dose trials

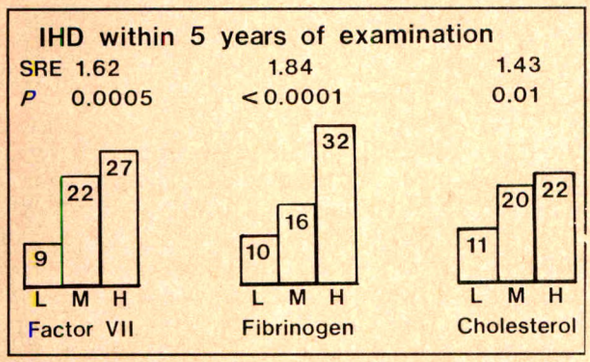


FIGURE 2. Numbers of events of ischemic heart disease (IHD) (fatal and nonfatal) within 5 years of examination by low (L), middle (M) and high (H) thirds of distributions of factor VII activity, fibrinogen, and cholesterol at entry to the Northwick Park Heart Study. Standardized regression effects (SRE) show the increase in risk of an event for a standard deviation increase: e.g., a 1 standard deviation increase in factor VII activity increases the risk of an event within 5 years by 62%. (Reproduced with permission from *Lancet*.[5])

Furthermore, it is likely that in some of the secondary prevention trials the intensity of anticoagulation was a good deal less than intended. If so, this provides the first indication that lower intensities than those usually aimed for may be effective.

Second, there is growing evidence that the level of factor VII coagulant activity, VII_c, is associated with the risk of IHD. Factor VII is the procoagulant clotting factor whose activity is most rapidly and extensively reduced by warfarin.

Figure 2 summarizes the results of the prospective Northwick Park Heart Study.[5] Besides the expected relation between cholesterol and IHD incidence, increasing levels of both VII_c and fibrinogen were associated with increased risk.

These relations have now been confirmed in the preliminary findings of another prospective study.[6] A growing number of cross-sectional studies also show a relation between the VII_c level and IHD or the risk of IHD.[7–10] Besides suggesting that VII_c may be involved in the pathogenesis of IHD, these findings also raise the possibility of reducing risk by lowering the VII_c level. The general epidemiologic characteristics of VII_c, including the effects of dietary fat intake, are all consistent with the hypothesis that high VII_c levels do contribute to the onset of IHD.[11]

Third, the VII_c level probably influences the rate of thrombin production.[11,12] Added to these experimental results is the value of factor VII concentrates in treating factor VIII-resistant hemophiliacs,[13] an approach that is presumably successful because of enhanced extrinsic pathway activity on thrombin production.

Finally, 4 randomized controlled trials have now demonstrated that lower intensities of oral anticoagulation are equally effective in preventing perioperative venous thrombosis after surgery[14–16] or thromboembolism after tissue heart-valve replacement,[17] but, as expected, with less bleeding than with conventional intensities.

For a variety of reasons, therefore, it is reasonable to ask whether, in carefully selected men at high risk of IHD, a relatively modest degree of oral anticoagulation with warfarin would reduce the incidence of IHD without increasing the risk of serious bleeding.

ASPIRIN

The case for aspirin in the primary prevention of IHD is much more familiar and less controversial—although still open.

The prolonged effect of aspirin on the secondary phase of platelet aggregation is well known. There is no doubt about the value of aspirin in those who have already had clinical vascular disease, whether MI, transient ischemic attacks or unstable angina pectoris.[18]

With regard to primary prevention, the recently reported preliminary findings from the trial in doctors in the United States[19] showed a significant reduction due to aspirin in the incidence of IHD. There was no obvious effect in the trial in British doctors,[20] although the results were not incompatible with those of the American trial. Both trials raised the possibility of increased risk of cerebral hemorrhage due to aspirin. Neither trial used aspirin doses that would be considered "low" according to current thinking. The dose in the American trial was 325 mg on alternate days, and in the British trial it was 500 mg/day for most participants.

Both trial populations were at low risk of IHD. The question of whether low doses of aspirin in men at high risk might be effective against IHD without an increase in the risk of bleeding therefore remains open.

COMBINED PROPHYLAXIS

Would warfarin and aspirin together reduce the incidence of IHD more than either agent on its own, and without inducing unacceptable bleeding?

Figure 3 summarizes the findings of the International

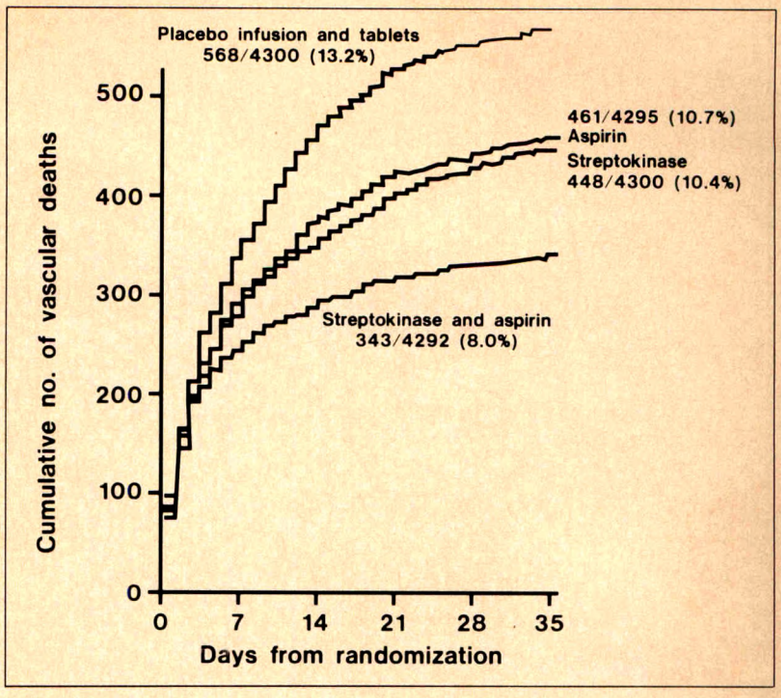


FIGURE 3. Cumulative vascular mortality in days 0 to 35. (Reprinted with permission from *Lancet*.[5])

Study of Infarct Survival (ISIS-2) trial of streptokinase and aspirin (160 mg/day) immediately after suspected MI.[21] Used separately, both streptokinase and aspirin reduced cardiovascular mortality over the 35-day period by about 20%. When they were used together, the reduction was over 40%. These results support the case for primary prevention by simultaneously modifying platelet function and fibrin formation (by oral anticoagulation rather than streptokinase).

In ISIS-2, anticoagulation (heparin or oral agents, or both) was planned for over 11,000 of the participants, and in most cases these plans were implemented. Among these patients the incidence of major bleeding episodes was no higher in those who took aspirin during the trial than in those who did not (personal communication from ISIS-2 investigators). This suggests that the concurrent use of anticoagulants and aspirin may not be as hazardous as is often assumed.

A special study undertaken during the planning of the Thrombosis Prevention Trial (TPT, see later) showed that anticoagulation of the intensity aimed for in TPT (International Normalized Ratio [INR] of about 1.5) with 75 mg aspirin did not increase the rate of gastric bleeding above the very low level attributable to this dose of aspirin.[22]

Finally, the pooled experience of 3 trials of patients undergoing valve replacement[23-25] indicates a high degree of effectiveness from concurrent use of warfarin and aspirin in conventional doses in preventing thromboembolism. Any risk of bleeding was confined mainly to the gastrointestinal tract.

In summary, therefore, the combined use of warfarin and aspirin may be particularly effective and will not necessarily lead to unacceptable levels of bleeding. This is particularly significant if we keep in mind that in a trial such as TPT the greatest risk facing participants is major events of IHD, about 50% of which are fatal.

THROMBOSIS PREVENTION TRIAL

The objective of this factorial trial[26] is to demonstrate a 30% reduction in the incidence of IHD in men at high risk, attributable to low-dose warfarin or low-dose aspirin, or both. One group will receive active warfarin and active aspirin. The aim of the warfarin component is to reduce VII_c from a high-risk level of about 120% to about 70%, the VII_c level characteristic of patients with little or no IHD. Full anticoagulation reduces VII_c to about 30%.

The TPT is being carried out through the British Medical Research Council's General Practice Research Framework. This framework was originally established for the mild hypertension trial of the Medical Research Council Working Party[27]; it has now been enlarged for other studies that can most appropriately be performed through general practice.

The first step for each practice is a search of all the notes of men aged 45 to 69 years, to permit exclusion of all those whose participation would be contraindicated—e.g., because of a recent history of peptic ulceration or because of alcohol abuse.

Those who remain eligible are then invited to a screening examination at which smoking status and family history are elicited, body mass index and blood pressure are determined, and cholesterol, fibrinogen and VII_c levels are measured. Each of these risk variables is then weighted according to its association with IHD in the Northwick Park Heart Study. Those men in the top 20% of the risk-score distribution are invited to take part in the treat-

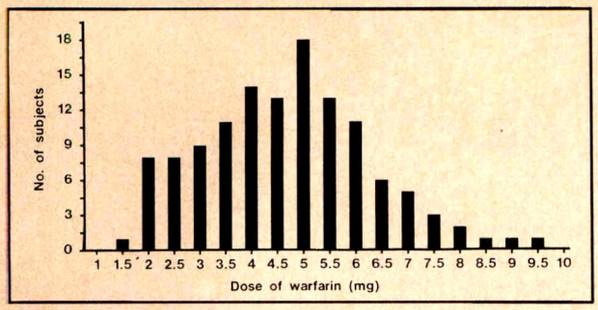


FIGURE 4. Distribution of stable warfarin doses. (Reprinted with permission from *Eur Heart J.*[26])

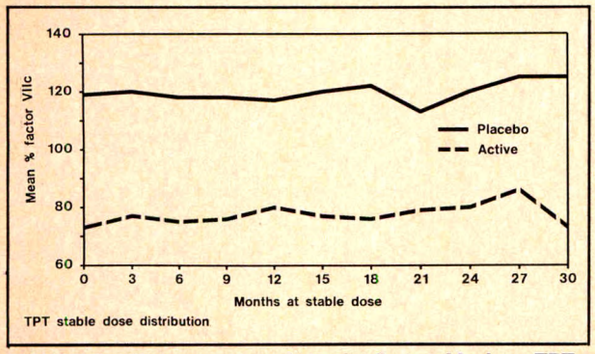


FIGURE 5. VII_c (percentage of standard) at stable dose. TPT = Thrombosis Prevention Trial. (Reprinted with permission from *Eur Heart J.*[26])

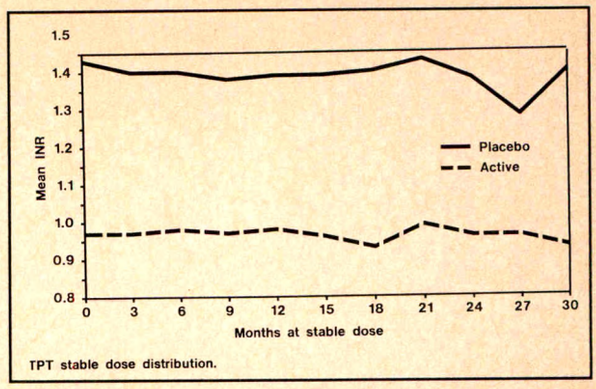


FIGURE 6. International Normalized Ratio (INR) at stable dose. TPT = Thrombosis Prevention Trial. (Reprinted with permission from *Eur Heart J.*[26])

TABLE II Numbers of Men Ever Reporting Symptoms

	Any Dose		Stable Dose	
	Active	Placebo	Active	Placebo
Nose bleed	21	21	12	15
Red/pink urine	2	5	0	3
Rectal bleeding	17	11	11	8
Bruising	17	10	11	5
Total no. of men	215	226	148	158

Some men report more than 1 symptom.

TABLE III Numbers of Episodes of Reported Symptoms

	Any Dose		Stable Dose	
	Active	Placebo	Active	Placebo
Nose bleed	38	46	23	28
Red/pink urine	2	5	0	3
Rectal bleeding*	41 (p = 0.04)	24	29 (p = 0.03)	16
Bruising	18	14	12	5
Total no. of questionnaires	2,180	2,187	1,143	1,288

* One man receiving active treatment accounted for 10 of the 41 episodes at any dose and 7 of the 29 episodes at stable dose.
The slightly larger number of questionnaires at stable dose from men receiving placebo treatment is the expected interim consequence of the procedure for matching patients receiving active and placebo treatment.

ment phase. Just over 70% of those invited for screening attend, and about the same proportion of those eligible for treatment enter the trial.

Treatment is double-blind; monitoring of the prothrombin time (expressed as INR) and dose regulation are performed from the coordinating center. Anticoagulation is induced with a starting dose of 2.5 mg of warfarin (or placebo) daily, increasing by 0.5 or 1.0 mg/day at monthly intervals until the appropriate stable dose for each man has been achieved. The average dose is 4.6 mg/day, but the doses range widely, as expected, from 1.5 to 10.0 mg/day (see Fig. 4). Figures 5 and 6 show that there has been no difficulty in achieving the VII_c objective of about 70%, corresponding to an INR of about 1.5.

Thus far (Table II), there is no difference in the numbers of men ever reporting nose bleeds, possible hematuria, rectal bleeding, or bruising at stable dose. The frequency (Table III) of rectal bleeding (but not any of the other 3 symptoms) is greater in those receiving active treatment. In other words, whereas treatment does not increase the number of men who ever report rectal bleeding, it does increase the frequency of bleeding in those who do report it.

The aspirin component of the trial has just been introduced as a 75-mg controlled-release preparation whose main effect is presystemic, maximizing the inhibition of thromboxane while minimizing the effect on prostacylin.

It is hoped that the 6,000 men required for the trial will have been recruited by the end of 1990 or early 1991.

Each man's participation will be for a minimum of 5 years.

CONCLUSION

In circumstances in which it is difficult or impossible to achieve the primary prevention of IHD through lifestyle modifications, pharmacologic methods have to be considered. Given the difficulty of achieving regression of atheroma, the most effective approach may be through prevention of thrombosis. There is increasing interest in the possibility that this may be achieved by the concurrent modification of fibrin formation and platelet function, using low doses of warfarin and aspirin that do not result in an unacceptable level of bleeding.

REFERENCES

1. International Anticoagulant Review Group. Collaborative analysis of long-term anticoagulant administration after acute myocardial infarction. *Lancet 1970;1:203–209.*

2. Chalmers TC, Matta RJ, Smith H, Kunzler A-M. Evidence favoring the use of anticoagulants in the hospital phase of acute myocardial infarction. *N Engl J Med 1977;297:1091–1096.*

3. Medical Research Council. An assessment of long-term anticoagulant administration after cardiac infarction. *Br Med J 1964;2:837–843.*

4. Sixty-Plus Reinfarction Study Research Group. A double-blind trial to assess long-term oral anticoagulant therapy in elderly patients after myocardial infarction. *Lancet 1980;2:989–994.*

5. Meade TW, Mellows S, Brozovic M, Miller GJ, Chakrabarti RR, North WRS, Haines AP, Stirling Y, Imeson JD, Thompson SG. Haemostatic function and ischaemic heart disease: principal results of the Northwick Park Heart Study. *Lancet 1986;2:533–537.*

6. Balleisen L, Schulte H, Assmann G, Epping P-H, van de Loo J. Coagulation factors and the progress of coronary heart disease (letter). *Lancet 1987;2:461.*

7. Dalaker K, Hjermann I, Prydz H. A novel form of factor VII in plasma from men at risk for cardiovascular disease. *Br J Haematol 1985;61:315–322.*

8. Dalaker K, Smith P, Arnesen H, Prydz H. Factor VII-phospholipid complex in male survivors of acute myocardial infarction. *Acta Med Scand 1987;222:111–116.*

9. Carvalho de Sousa J, Azevedo J, Soria C, Barros F, Ribeiro C, Parreira F, Caen JP. Factor VII hyperactivity in acute myocardial thrombosis. A relation to the coagulation activation. *Thromb Res 1988;51:165–173.*

10. Hoffman C, Shah A, Sodums M, Hultin MB. Factor VII activity state in coronary artery disease. *J Lab Clin Med 1988;111:475–481.*

11. Meade TW. The epidemiology of haemostatic and other variables in coronary artery disease. In: Verstraete M, Vermylen J, Lijnen R, Arnout J, eds. Thrombosis and Haemostasis 1987. *Leuven: Leuven University Press, 1987;37–60.*

12. Miller GJ, Seghatchian MJ, Walter SJ, Howarth DJ, Thompson SG, Esnouf MP, Meade TW. An association between the factor VII coagulant activity and thrombin activity induced by surface/cold exposure of normal human plasma. *Br J Haematol 1986;62:379–384.*

13. Hedner U, Glazer S, Pingel K, Alberts KA, Blomback M, Schulman S, Johnsson H. Successful use of recombination factor VIIa in patient with severe haemophilia-A during synovectomy (letter). *Lancet 1988;2:1193.*

14. Hull R, Hirsh J, Jay R, Carter C, England C, Gent M, Turpie AGG, McLoughlin D, Dodd P, Thomas M, Raskob G, Ockelford P. Different intensities of oral anticoagulant therapy in the treatment of proximal-vein thrombosis. *N Engl J Med 1970;2:203–209.*

15. Francis CW, Marder VJ, McCollister Evarts C, Youkoolbodi S. Two-step warfarin therapy. Prevention of post-operative venous thrombosis without excessive bleeding. *JAMA 1983;249:374–378.*

16. Poller L, McKernan A, Thompson JM, Elstein M, Hirsch PJ, Jones JB. Fixed minidose warfarin: a new approach to prophylaxis against venous thrombosis after major surgery. *Br Med J 1987;295:1309–1312.*

17. Turpie AGG, Hirsh J, Gunstensen J, Nelson H, Gent M. Randomised comparison of two intensities of oral anticoagulant therapy after tissue heart valve replacement. *Lancet 1988;1:1242–1245.*

18. Antiplatelet Trialists' Collaboration. Secondary prevention of vascular disease by prolonged antiplatelet treatment. *Br Med J 1988;296:320–331.*

19. The Steering Committee of the Physicians' Health Study Research Group. Preliminary report: findings from the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med 1988;318:262–264.*

20. Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K, Warlow C, Hafner B, Thompson E, Norton S, Gilliland J, Doll R. Randomised trial of prophylactic daily aspirin in British male doctors. *Br Med J 1988;296:313–316.*

21. ISIS-2 Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither, among 17,187 cases of suspected acute myocardial infarction: ISIS-2 *Lancet 1988;2:349–360.*

22. Prichard PJ, Kitchingman GK, Walt RP, Daneshmend TK, Hawkey CJ. Human gastric mucosal bleeding induced by low dose aspirin, but not warfarin. *Br Med J 1989;298:493–496.*

23. Altman R, Boullon F, Rouvier J, Raca R, de la Fuente L, Favaloro R. Aspirin and prophylaxis of thromboembolic complications in patients with substitute heart valves. *J Thorac Cardiovasc Surg 1976;72:127–129.*

24. Dale J, Myhre E, Loew D. Bleeding during acetylsalicylic acid and anticoagulant therapy in patients with reduced platelet reactivity after aortic valve replacement. *Am Heart J 1980;99:746–752.*

25. Chesebro JH, Fuster V, Elveback LR, McGoon DC, Pluth JR, Puga FJ, Wallace RB, Danielson GK, Orszulak TA, Piehler JM, Schaff HV. Trial of combined warfarin plus dipyridamole or aspirin therapy in prosthetic heart valve replacement: danger of aspirin compared with dipyridamole. *Am J Cardiol 1983;51:1537–1541.*

26. Meade TW, Wilkes HC, Stirling Y, Brennan PJ, Kelleher C, Browne W. Randomized controlled trial of low dose warfarin in the primary prevention of ischaemic heart disease in men at high risk: design and pilot study. *Eur Heart J 1988;9:836–843.*

27. Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *Br Med J 1985;291:97–104.*

New Approaches to Treatment of Myocardial Infarction

James H. Chesebro, MD, Lina Badimon, PhD, and Valentin Fuster, MD

Survival of patients with acute transmural infarction is largely related to the size of the myocardial infarction. The goal of thrombolytic therapy in acute myocardial infarction is maximal salvage of myocardium by reestablishment of flow in the occluded infarct-related artery and the establishment and maintenance of a patent infarct-related artery. Results of randomized trials show a significant reduction in mortality in patients who have undergone thrombolysis. A patent infarct-related artery, even in the absence of a change in left ventricular function, is associated with reduced mortality. The Thrombolysis in Myocardial Infarction Trial and the European Cooperative Trial showed that recombinant tissue-type plasminogen activator is superior to streptokinase in reestablishing flow in a totally occluded artery.

Experimental and clinical evidence suggests that thrombolysis and thrombosis occur simultaneously, and that lysis appears to increase both thrombin and platelet activity. Effective reduction of thrombosis accelerates thrombolysis. Rethrombosis after thrombolysis is due to anchored residual thrombus, which alters the hemorrheology of blood flow and produces a highly thrombogenic substrate that is largely due to residual fibrin-bound thrombin. Platelet deposition is directly related to severity of residual stenosis and shear rate.

Thrombin appears to be the most potent of the 5 potential stimulators of platelet activation during arterial thrombosis. Proper anticoagulation can play an important role in reducing thrombosis. Experimental evidence strongly supports the use of heparin during and after thrombolysis. A recently reported study shows continued reduction of residual stenosis after 1 month of vigorous anticoagulation with intravenous heparin and subsequent oral anticoagulation. A recent clinical trial showed that subcutaneous heparin given during hospitalization reduced recurrent ischemia after thrombolysis, mortality and left ventricular mural thrombosis.

Most current trials are using both heparin and aspirin during and after thrombolysis, with apparent reduction in rates of reocclusion. Thrombolysis with a combination of recombinant tissue-type plasminogen activator and either streptokinase or urokinase appears to reduce reocclusion. Maximal therapy to enhance continued lysis of residual mural thrombus after hospitalization includes combined anticoagulation with sodium warfarin and probably low-dose aspirin at 80 mg/day.

(Am J Cardiol 1990;65:12C–19C)

From the Mayo Clinic, Rochester, Minnesota.

Address for reprints: James Chesebro, MD, Mayo Clinic, 200 First Street, SW, Rochester, Minnesota 55905.

Treatment of myocardial infarction (MI) in the coronary care unit has decreased hospital mortality from 30 to 10%, largely because of improvements in the treatment of acute arrhythmias, made possible in the coronary care unit. The survival of patients with acute transmural MI is now related to the size of the infarction and probably to patency of the infarct-related artery.

Although reduction of myocardial demand can slow the rate of infarction, reperfusion is necessary for the ultimate salvage of myocardium.[1] DeWood and co-workers'[2] landmark studies showed that coronary thrombosis with total occlusion is present in approximately 80% of infarct-related arteries within the first 6 hours after onset of symptoms, and that beyond 6 hours this incidence decreases approximately one fourth, to 60%—probably because of spontaneous reopening. Their findings suggested that thrombolytic therapy is the most rational approach for achievement of rapid and noninvasive reperfusion.

This article focuses on thrombosis and thrombolysis in acute MI. It reviews patient selection; reperfusion goals and end points; simultaneous lysis and thrombosis; rethrombosis and residual thrombus—the roles of arterial substrate and rheology, thrombin, anticoagulation, and the interaction between platelets and clotting factors; current recommendations; and future prospects.

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria for thrombolytic therapy for patients at risk of acute transmural MI include: (1) age younger than 76 years; (2) ST-segment elevation ≥0.1 mV in 2 of 3 inferior leads, 2 contiguous precordial leads, or leads I and aVL (not reversed by nitroglycerin); (3) 20 to 30 minutes of myocardial ischemic pain (not reversed by nitroglycerin); and (4) less than 4 to 6 hours elapsed time from the onset of ischemic pain to thrombolytic therapy. Among patients to whom criteria 2 and 3 apply, 99% will have acute MI.[3]

Exclusion criteria for thrombolytic therapy include: (1) prolonged time from onset of ischemic pain (more

than 6 to 12 hours, unless there is persistent pain and continued ST-segment elevation); (2) age older than 75 years; (3) uncontrolled hypertension (>180/110 mm Hg) at any time during emergency room evaluation; (4) left ventricular hypertrophy on electrocardiogram; (5) previous cerebrovascular event or transient ischemic attack; (6) prolonged cardiopulmonary resuscitation, or noncompressive procedural site such as bladder, or bowel fulguration, or polyp removal; (7) left bundle branch block; (8) active hemorrhage or history of bleeding diathesis; (9) dilated cardiomyopathy or oral anticoagulation; (10) advanced or terminal illness; and (11) women of childbearing potential.[3]

Previous coronary bypass surgery is not a contraindication, since acute thrombotic occlusion may occur in these patients, especially beyond 3 years postsurgery. Cardiogenic shock is an indication, because reperfusion appears critical for its reversal.

GOALS OF THROMBOLYTIC THERAPY

The goals and end points of reperfusion are: (1) reestablishment of flow in the occluded infarct-related artery (minutes to hours); (2) improvement in left ventricular function (days) or, even better, maximal salvage of myocardium in jeopardy, as determined by computerized tomographic evaluation of perfused viable myocardium before and after thrombolysis; and (3) reduction in mortality (days to weeks).

INCIDENCE OF REPERFUSION

In early, smaller studies, all of which involved intravenous streptokinase, the true incidence of reperfusion was problematic for a number of reasons:

1. Patency was confused with reperfusion. Thus, although baseline angiography usually showed total occlusion, only subtotal occlusion was present in 5 to 31% of patients.

2. Time until the follow-up angiogram assessing reperfusion or patency varied in different groups and studies.

3. A variable patient population meant that when baseline angiography was not used as an inclusion criterion, the population might have included patients with subtotal occlusion, and electrocardiographic criteria also varied between studies (ST-segment elevation, depression or undefined).

4. Reperfusion was often undefined or included transient reperfusion that was followed by reocclusion within the first 90 minutes.

The Thrombolysis in Myocardial Infarction (TIMI-1) trial clarified the measurement of reperfusion by establishing 4 grades as criteria for baseline occlusion and subsequent reperfusion.

Grade 0 represented no reperfusion or no flow beyond the point of occlusion; grade 1, partial penetration of contrast beyond the obstruction, but incomplete filling of the infarct-related artery; grade 2, partial reperfusion, or contrast that opacified the entire distal coronary artery, but with a slow rate of entry or clearance compared with a totally normal artery; and grade 3, complete reperfusion, which means complete and prompt filling and clearance of contrast media from the coronary artery.

The TIMI-1 trial, in which baseline angiography was performed in every patient before treatment, measured the incidence of reperfusion of infarct-related arteries with human recombinant tissue-type plasminogen activator (rt-PA) and with streptokinase. Reperfusion was achieved in more than 60% of patients, both in those who presented within 3 hours of onset of ischemic pain and in those who presented more than 3 hours after onset. The incidence of reperfusion was significantly lower with streptokinase than with rt-PA within 3 hours of onset, but especially beyond the 3-hour range.[3]

The TIMI-1 trial results were confirmed by the European Cooperative Study Group, which analyzed patency results for rt-PA and streptokinase both within and beyond 3 hours. The difference in the 3-hour patency rates for rt-PA and streptokinase was of borderline significance ($p = 0.06$) in both the TIMI-1 and European trials; however, when data from the 2 are combined, the difference in favor of rt-PA is highly significant both for patients treated within and beyond 3 hours. Thus, rt-PA appears superior to streptokinase in reestablishing flow in a totally occluded artery.[3–5]

The incidence of reperfusion is significantly greater (63% for streptokinase, 90% for rt-PA) with any of the lytic agents when the baseline perfusion is grade 1 (contrast media penetrating and extending beyond the obstruction, but not completely filling the artery) rather than grade 0—suggesting that there is a lesser volume of thrombus that requires lysis before complete reperfusion.[3,6]

EFFECT ON MORTALITY

Results of randomized trials in patients undergoing thrombolysis (all but 3 using streptokinase and the others using intravenous anisoylated plasminogen streptokinase activator complex [APSAC] or rt-PA) also show a significant reduction in mortality.[7–13] In the International Study of Infarct Survival (ISIS-2), streptokinase alone reduced mortality from 13.2% in the placebo group to 10.4%; but the addition of aspirin to streptokinase reduced mortality to 8%. Presumably, aspirin reduced the incidence of reocclusion and may have enhanced thrombolysis. However, these results are not altogether clear, since admission criteria for ISIS-2 included ST-segment depression or no electrocardiographic changes at all. The study thus appears to have included a significant number of patients with nontransmural MI and unstable angina. In these patients, the indication for thrombolysis, if any, is not clear. In addition, 50% of the patients received heparin which reduced mortality (nonrandomized, retrospective analysis) in ISIS-2. Mortality with rt-PA was reduced in 2 trials (from 9.8 to 7.2% and from 5.7 to 2.8%).[12,13]

EVIDENCE FOR LYSIS AND THROMBOSIS AS ONGOING, SIMULTANEOUS PROCESSES

Electrophoretic, immunologic, chemical and clinical evidence suggests that thrombolysis and thrombosis are

TABLE I Relation Between Platelet Deposition, Substrate and Severity of Stenosis

Stenosis %	0		80	
Substrate	Deep arterial injury	Residual thrombus	Deep arterial injury	Residual thrombus
PD* (n = 10)	22 ± 6	40 ± 7	66 ± 18	219 ± 61

* PD = platelet deposition × $10^6/cm^2$.
Adapted from *Circulation*.[27]

dynamic processes that occur simultaneously. Lysis appears to increase both thrombin and platelet activity. Both streptokinase and rt-PA increase plasma and urinary thromboxane A_2 metabolites (evidence of increased platelet activity) and plasma levels of fibrinopeptide A (evidence of increased thrombin activity). Mechanisms for this may be exposure of thrombin bound to fibrin and activation of factor V to Va by plasmin.[14–18] As will be discussed later, activated factor V (Va) is a necessary component of the prothrombinase complex, which is the major pathway of thrombin formation.

There is further experimental evidence indicating that thrombolysis and thrombosis occur simultaneously. In experimental studies, effective reduction of thrombosis accelerates thrombolysis. Heparin administered in a dosage of 200 U/kg enhances lysis with streptokinase, urokinase and rt-PA.[19,20] Specific thrombin inhibition enhances lysis by rt-PA by more than 50%.[21] Potent monoclonal antiplatelet antibodies to the specific membrane receptor glycoprotein IIb/IIIa (which binds platelets together through a fibrinogen molecule link) accelerate thrombolysis by rt-PA.[21,22] Antiplatelet therapy with receptor inhibition for thromboxane A_2 and serotonin enhances thrombolysis in dogs with subendothelial arterial injury (a mild stimulus for thrombosis).[23]

MECHANISMS OF THROMBUS FORMATION

The extent of platelet deposition, and thus the formation of a macroscopic thrombus acutely within an artery, depends on the severity of arterial injury. Mild or subendothelial injury that only denudes the endothelium leads to limited platelet deposition (a single layer). However, deep arterial injury such as occurs in acute infarction—in which the injury extends into the media (below the internal elastic lamina) or involves the rupture of a plaque—leads to multilayered, unlimited numbers of platelets deposited, and thus to the formation of a macroscopic thrombus.[24]

The possible sequelae of an arterial mural thrombus are: (1) growth to total occlusion; (2) distal embolization of tiny thrombi, which have been shown to produce regions of micronecrosis in patients who die after unstable angina; (3) organization of the mural thrombus to produce growth of the atherosclerotic plaque; or (4) complete lysis or dissolution, which is the most desirable outcome. The latter can occur in the presence of adequate antithrombotic therapy, which permits endogenous lysis.

MECHANISMS OF REOCCLUSION AFTER THROMBOLYSIS

The incidence of reocclusion after thrombolysis is approximately 8% within the first 24 hours and 10 to 20% overall during hospitalization. Rethrombosis is partly related to the thrombolytic agent; it appears to be related to the adequacy of thrombolysis and the residual minimal diameter of the infarct-related artery at 90 minutes, and is probably related to the adequacy of antithrombotic therapy.[25,26]

In rethrombosis due to anchored residual thrombus, the bulk of the residual thrombus produces a persistent stenosis that alters the rheology of blood flow. In addition, this produces a thrombogenic substrate that is even more thrombogenic than the deeply injured arterial wall.[26,27]

Continuous scintigraphic counting of ^{111}In-labeled platelet activity shows a steady growth of the thrombus, which suddenly drops off because of distal embolization, and then results in extremely rapid regrowth. Why does this regrowth occur? Residual mural thrombus is more thrombogenic than deeply injured arterial wall, and the residual stenosis potentiates this thrombosis (Table I). In an ex vivo perfusion chamber with arterial blood flowing directly from the animal through the chamber at a constant flow, platelet deposition is considerably lower in the presence of deep arterial injury than when the substrate is residual thrombus, even in the absence of a stenosis. In the presence of an 80% stenosis, platelet deposition is higher on the deeply injured artery, but is highest by far on residual thrombus.[26,27]

Platelet deposition within a stenosis is maximal within the minimal diameter of the stenosis; the thrombus is less platelet-rich proximal and distal to the stenosis. In addition, as the severity of the stenosis increases, there is a marked increase in platelet deposition.[24,26,27]

Platelet deposition is dependent on the shear rate. Shear rate is the difference, in blood flow, between the fluid or cell velocity at the center of the artery and the velocity at the periphery. It is directly related to blood flow and inversely related to the third power of the lumen diameter. Two factors appear to explain why high shear rate leads to increased platelet deposition: Higher shear rates appear to increase adenosine diphosphate (ADP) at the surface of the platelet, and at high shear rates red cells force platelets to the periphery of the artery.[24,26,28]

In the presence of mild or superficial arterial injury (endothelial denudation only), platelet deposition is not well anchored, easily washes away, reaches a ceiling or plateau over time, and does not increase. However, in the presence of deep arterial injury there is a continued increase in platelet deposition over time, at a rate that is directly related to the shear force.[24,26,29] Several studies have shown that the incidence of reocclusion after thrombolysis is related to the residual coronary stenosis at 90 minutes. This relation has been demonstrated by measuring the minimal cross-sectional area, diameter, or percent of stenosis of the residual lesion; all of these predict higher rates of reocclusion for high-grade residual lesions than for less severe lesions.[25]

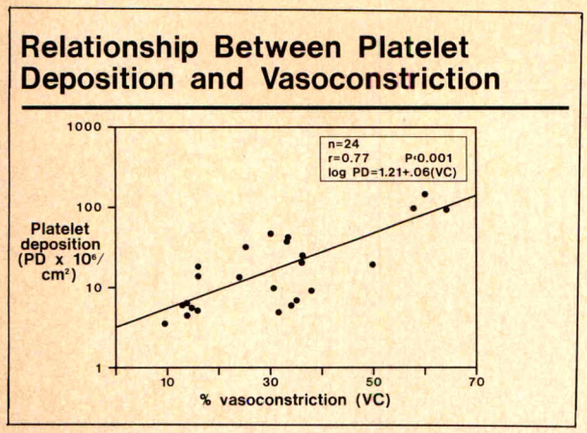


FIGURE 1. In an experimental pig model, the severity of vasoconstriction following arterial injury produced by arterial angioplasty was directly related to the log of the platelet deposition. (Adapted from *Circulation.*[30])

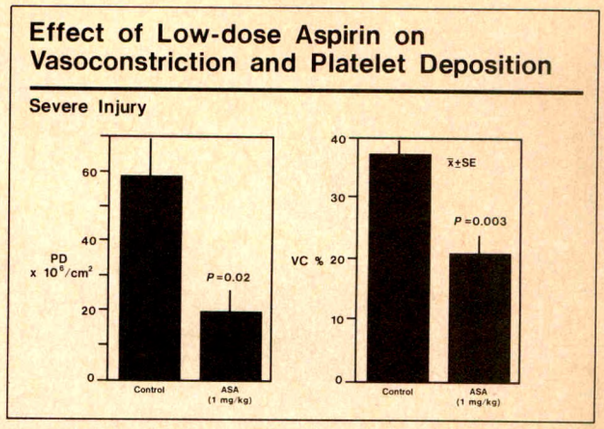


FIGURE 2. The degrees of both vasoconstriction and platelet deposition (PD) in an experimental pig model of acute arterial injury are reduced with low-dose aspirin (ASA). SE = standard error. (Adapted from *Circulation.*[30])

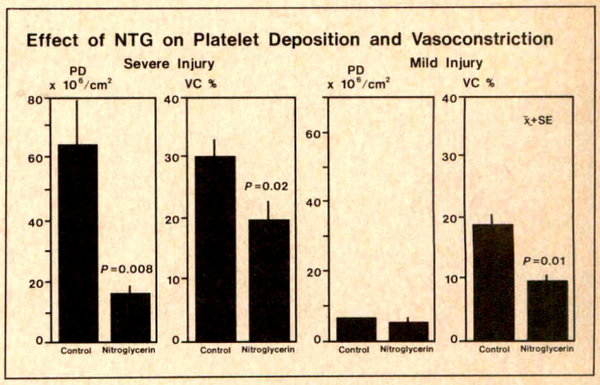


FIGURE 3. In the pig model of arterial injury, nitroglycerin (NTG) achieved significant reduction in both vasoconstriction (VC) and platelet deposition (DP) in severe injury. (Adapted from *Circulation.*[31])

VASOCONSTRICTION AND PLATELET DEPOSITION

Vasoconstriction of the artery also contributes to the severity of residual stenosis after acute arterial injury. Experimentally, the severity of vasoconstriction is directly related to the log of the platelet deposition (Fig. 1). The degrees of both acute vasoconstriction and platelet deposition associated with deep arterial injury are reduced by a platelet inhibitor that has no vasodilatory effects (but can block synthesis of thromboxane A_2) such as low-dose aspirin at 1 mg/kg/day (Fig. 2).[30]

In studies performed in a pig model, intravenous nitroglycerin, titrated to reduce the mean arterial pressure by 10 mm Hg during acute arterial injury, reduced the degree of vasoconstriction, as expected, in both deeply and mildly injured arteries; surprisingly, it also significantly reduced platelet deposition in deeply injured arteries (Fig. 3).[31] Vasodilation with nifedipine or verapamil did not result in decreased platelet deposition.

Vasodilatation with other drugs, such as receptor blockers for serotonin or thromboxane A_2, significantly reduced vasoconstriction but not platelet deposition in the presence of deep arterial injury.[32]

REDUCTION OF RESIDUAL THROMBUS WITH ANTICOAGULATION

At 90 minutes after reperfusion of an infarct-related artery, residual thrombus is frequently seen trailing distally beyond the area of stenosis. This resolves within the following 24 hours in about 50% of patients but it may persist through most of the hospitalization period in others. In addition, with anticoagulation, further reduction of residual stenosis and improvement in the minimal lumen diameter of the infarct-related artery has been shown to occur between the time of lysis and hospital discharge.[3,33]

Nakagawa et al[34] reported continued improvement of the infarct-related artery, with reduction of residual stenosis after 1 month of rigorous anticoagulation with intravenous heparin and subsequent oral anticoagulation. They also recognized the development of extraluminal contrast pooling in an ellipsoid shape (type A), single or paired linear radiolucencies with or without outpouching (type B), and with definite outpouching (type C). Throughout the study, at least 1 type of the A-C lesions developed in over half the patients. The tendency was for lesion development to proceed from total or severe occlusion to type A and then to type B or C, both of which were accompanied by progressive reduction in luminal narrowing and by frequent enlargement of the outpouching. Postmortem examination in 1 patient with a type B lesion showed a ruptured atherosclerotic plaque with adjacent paired ridges.[34]

These findings confirm the expected presence of residual thrombus after thrombolysis, with further lysis occurring over time with anticoagulation. In conjunction with the experimental and clinical data, these findings also suggest a probable future tendency in clinical practice to use longer-term anticoagulation after thrombolysis, with the objective of reducing residual thrombus.

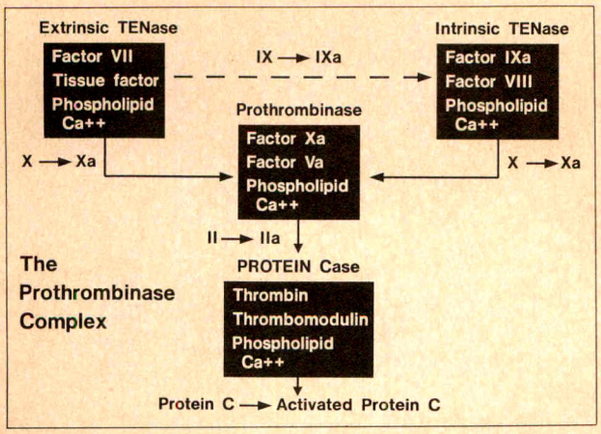


FIGURE 4. The major pathway of thrombin formation is via the prothrombinase complex, consisting of activated factors Xa, Va, Ca^{++} and phospholipid.[39]

Given this likely direction in future practice, one should keep in mind that the half-life of bolus intravenous heparin is dose-dependent and may vary from 30 to 80 minutes, depending on patient status. The shorter half-life occurs at lower doses such as 3,000 U; the longer half-life occurs after a moderate bolus such as 10,000 U. The important principle is that heparin plasma levels decrease rapidly, especially after the initial bolus, in part because heparin binds to endothelial receptors, and a significant proportion of the initial bolus is necessary to saturate these receptor-binding sites. Heparin levels can be maintained by using an initial bolus followed by a constant infusion.[35]

ROLE OF THROMBIN IN ARTERIAL THROMBOSIS

In an initial retrospective study that we conducted in pigs receiving different dosages of heparin, there was an inverse relation of the log of platelet deposition with increasing heparin dosage.[36] In a subsequent prospective randomized study using 6 different dosages of heparin at the time of deep arterial injury, quantitative platelet deposition steadily decreased as the dosage of heparin increased. Similarly, quantitative fibrinogen deposition decreased at higher dosages of heparin compared with deposition at lower dosages. We hypothesized that heparin's antithrombin effects accounted for its increased effectiveness at higher dosages. To test this hypothesis, we used the specific thrombin inhibitor hirudin, which is the anticoagulant of the European leech (*Hirudinea medicinalis*). Hirudin significantly decreased quantitative platelet and fibrinogen deposition even more than the highest dosage of heparin, suggesting that thrombin plays a critical role in arterial thrombosis.[37]

We also found that the incidence of macroscopic mural thrombi was steadily reduced as heparin dosage was increased, and that hirudin totally prevented mural thrombosis after deep arterial injury.[37] In our pig model, modest doses of heparin plus low-dose aspirin only reduced the incidence of mural thrombosis to 25% in deep arterial injury.[30] Inhibition of specific secondary activators of platelets, thromboxane A_2, serotonin, or both, using receptor inhibitors, did not decrease platelet deposition.[38] This also emphasizes the critical role of thrombin in arterial thrombosis.

How is the major portion of thrombin generated? The major pathway of thrombin formation is via the prothrombinase complex. This complex is composed of activated factors X (Xa) and V (Va) and calcium, which are all bound to the phospholipid of the platelet membrane (Fig. 4).[39]

When all 4 of these factors (Xa, Va, Ca^{++} and phospholipid) are present, the rate of thrombin formation is 278,000 times greater than the rate of thrombin formation in the presence of any single factor alone (Table II). Thus, the prothrombinase complex is critical for amplification of the clotting system and thrombus formation.[39]

Of the 5 potential stimulators of platelet activation during arterial thrombosis (prostaglandins or thromboxane A_2, serotonin, ADP, collagen and thrombin), thrombin appears to be the most potent and critical, and it plays a key role. There is an important interrelation between the coagulation system and platelets via the prothrombinase complex. Thrombin plays a key role not only in the potent activation of platelets, but also in stabilizing the clot with the production of fibrin and in the cross-linkage of fibrin (via the activation of factor XIIIa). Proper anticoagulation can thus play an important role in reducing arterial thrombosis.[35,39]

Thrombosis can be activated by disturbance of the thrombus, by lysis, by mechanical disturbance such as a catheter, or after spontaneous embolization, all of which appear to expose active thrombin that is bound to fibrin within the thrombus. This creates a very active surface for rethrombosis. In addition, the thrombolysing enzyme, plasmin, activates factor V, which is an important component of the prothrombinase complex, and which, along with the platelet membrane, protects factor Xa from inhibition by antithrombin III. This plasmin stimulation of factor V activation probably also promotes thrombin production and rethrombosis.[17,35,39]

TABLE II Relative Rates of Prothrombin Activation in the Presence of Various Combinations of Components of the Prothrombinase Complex

Components Present	Relative Rate
Xa	1
Xa, PCPS	1
Xa, Ca^{++}	2
Xa, Ca^{++}, PCPS	22
Xa, Ca^{++}, Va	356
Xa, Ca^{++}, PCPS, Va	278,000
Xa, Ca^{++}, PCPS, V	695

PCPS = phosphatidylcholine-phosphatidylserine; Xa = activated factor X; Va = activated factor V.
Adapted from *Mann et al.*[39]

HEPARIN DURING AND AFTER THROMBOLYSIS

There are no randomized clinical trials testing the proper dosage or effectiveness of heparin during and after

thrombolysis. The dosage used in a recent report by Topol et al[40] probably was too low to achieve potentiation of thrombolysis. The study also involved too few patients to judge effectiveness. However, there is strong experimental evidence supporting use of heparin during and after thrombolysis.[16,18–20,25,26,36,37,39]

Experimentally, thrombus reaccumulated during infusion of rt-PA for coronary thrombosis in animals if heparin was discontinued. In addition, 200 U/kg of heparin enhanced experimental lysis with streptokinase, urokinase and rt-PA.[19,20] Heparin reduces platelet-to-platelet interaction when platelet deposition exceeds a monolayer, as demonstrated by Badimon and Fuster. (The heparin studies during deep arterial injury in our pig model were previously described.) In addition, Gold of Massachusetts General Hospital has found that heparin is needed, along with the potent platelet inhibitor antibody to glycoprotein IIb/IIIa, in order to prevent rethrombosis after thrombolysis in the presence of deep arterial injury (but not in the presence of superficial injury or deendothelialization, where the platelet inhibitor alone can prevent rethrombosis in the presence of stenosis and this mild thrombogenic stimulus).

EFFECT OF THROMBOLYTIC AGENTS ON INCIDENCE OF RETHROMBOSIS

The strongest evidence that the choice of thrombolytic agents also can affect the incidence of rethrombosis is from clinical studies of rescue angioplasty, i.e., acute angioplasty of the totally occluded infarct-related artery resistant to thrombolysis 90 minutes after initiation of lytic therapy. The reocclusion rate is characteristically high in this situation: When rt-PA alone was used, the reocclusion rate was 26 to 31%[41,42]; when urokinase was combined with rt-PA the rate was 4%.[43] In another study using streptokinase combined with rt-PA, with and without rescue angioplasty, the reocclusion rate was 9%.[44] Adjunctive therapy with heparin and aspirin was also used in all these studies.

FUTURE PROSPECTS

Future therapies may include platelet inhibition through platelet membrane glycoprotein inhibitors, such as inhibition of the von Willebrand factor by a specific antibody or protein-receptor blocker. The von Willebrand factor is responsible for platelet adhesion to the injured arterial wall, and for interplatelet binding through the specific platelet membrane receptors Ib and IIb/IIIa, respectively.[24,26] Whereas aspirin combined with heparin reduced platelet deposition in the ex vivo perfusion chamber by only 30%, antibody to the von Willebrand factor reduced platelet deposition by 80%, and the use of blood from pigs with homozygous von Willebrand disease reduced platelet deposition by 90%.[26,45]

Another prospect is the use of monoclonal antiplatelet glycoprotein IIb/IIIa antibody, which inhibits the interplatelet binding of fibrinogen at the end-stages of platelet aggregation.[26,46] This antibody inhibits platelet aggregation to collagen, thrombin and ADP, but markedly prolongs the bleeding time for more than 48 hours. It accelerated thrombolysis with rt-PA in an animal model with mild arterial injury.[47] It reduced arterial graft-associated platelet thrombosis within the body of the graft.[48] It prevented reocclusion after thrombolysis with rt-PA in the presence of mild injury, but it required the addition of heparin to prevent reocclusion after thrombolysis in the presence of deep arterial injury. Another group of investigators found that this antibody did not reduce thrombosis in arterial grafts placed in situ in baboons.[49] The conflicting results may relate to the problem of deep arterial injury at anastomotic sites, or to the investigators use of a less potent antibody which may or may not affect parallel ligand binding of von Willebrand factor.[24,26]

Simultaneous use of receptor blockers of thromboxane A_2 and serotonin reduced reocclusion in an animal model of mild arterial injury but left intact the most important pathway dependent on thrombin and collagen.[23,50] Thus, whether these agents are better than aspirin and effective in deep arterial injury remains to be proved.

Today most trials and most investigators are using both heparin and aspirin during and after thrombolysis; in uncontrolled studies this appears to have reduced reocclusion rates from the 15 to 20% range to the 5 to 10% range. Recurrent ischemia was reduced to a low incidence of <6% using heparin with the activated partial thromboplastin time (APTT) prolonged to 2 to 3 times control.[51] The importance of heparin was also emphasized in a group of patients treated with streptokinase and maintained with heparin therapy; the frequency of recurrent ischemia was inversely related to the level of anticoagulation and frequently occurred soon after discontinuation of heparin.[52] The use of combined thrombolytic agents appears promising for gaining benefit from improved acute opening with rt-PA (compared with streptokinase alone), prolonged lysis, reduced reocclusion and cost saving (if streptokinase is used). Thus, the addition to rt-PA of either streptokinase or urokinase has been found to reduce reocclusion to 9% or less and to provide a cost benefit by permitting the use of rt-PA for only the first hour. The reason for reduced reocclusion is probably multifactorial with the combination of heparin, aspirin, prolonged lysis, reduced plasma fibrinogen and increased fibrin-split products that also add to the anticoagulant effect. Maintenance infusion of rt-PA reduced reocclusion in a small controlled clinical trial in patients; however, the dosage of rt-PA required usually approached too large a dose (150 mg).[53] This high dose appears to increase the risk of cerebral bleeding. Experimentally, platelet inhibition alone has both accelerated thrombolysis and reduced reocclusion rates in the presence of superficial arterial injury; but the addition of heparin to platelet inhibition appears to be required in the presence of deep arterial injury which occurs with plaque rupture.

CURRENT RECOMMENDATIONS

Given currently available data, we offer the following guidelines for thrombolysis and the reduction of reocclusion with the caveat that most of these guidelines are

empirically based rather than conclusions from controlled clinical trials. Cost-effective successful lysis with lowest reocclusion rates may best be achieved with rt-PA, 1 mg/kg (up to 70 mg) over the first hour (with 10 mg given as the initial bolus), and with simultaneous streptokinase, 1.5 million intravenous units over 1 hour. Thrombolytic therapy is combined with heparin started immediately. Heparin significantly reduces early reocclusion, recurrent ischemic episodes, mortality, and in anterior myocardial infarction reduces the incidence of left ventricular mural thrombosis.[54–56] A heparin bolus of 150 U/kg is given with the lytic agents, and an infusion of 1,000 U/hour is started immediately to maintain heparin levels. The heparin infusion is adjusted, starting approximately 12 hours later, to maintain APTT at 2 to 3 times control for 3 to 5 days. APTT measurements obtained before 12 hours can be used to be sure that APTTs are not too low, requiring increased heparin dosage. However, APTT measurements should not be used to limit the heparin infusion below 1,000 U/hour, because thrombolysis can also contribute to prolonged APTT. Therapy with aspirin is begun immediately at a dosage of 160 mg/day and continued indefinitely. Empiric vasodilation with intravenous nitroglycerin, administered to reduce the mean arterial pressure by 10 mm Hg, may be helpful in reducing the incidence of associated arterial spasm, maximizing the minimal lumen diameter of the stenosis so as to reduce shear forces within the infarct-related artery and stenosis; and it may assist in platelet inhibition and a reduction of ongoing thrombosis and rethrombosis.[31]

Acute routine angioplasty does not appear to be necessary, and it may be detrimental by increasing the risk of rethrombosis; but it can be considered at any time in patients with ongoing or recurrent ischemia, or in the presence of a positive rehabilitation exercise test or clinical evidence for heart failure.[57–59] Maximal therapy to enhance continued lysis of residual mural thrombus includes combined anticoagulation with warfarin and low-dose aspirin at 80 mg/day (to maximize antithrombotic therapy and minimize the risk of bleeding) as suggested by new studies in unstable angina.[60,61] In patients who have no residual ischemia or evidence of severe residual stenosis, aspirin alone (160 mg/day) may suffice.

It is uncertain whether a future lytic agent will surpass the effectiveness of existing agents. However, combining potent antithrombin therapy with lytic agents appears very promising for both the acceleration of thrombolysis and the reduction of reocclusion. The associated roles of blockers of adhesive glycoproteins, such as the von Willebrand factor, or blockers of platelet glycoprotein receptors, such as antibody to glycoprotein receptor IIb/IIIa, need further investigation. The use of a specific thrombin inhibitor appears promising for both accelerating thrombolysis and blocking the platelet rich thrombosis that occurs in arteries[21,37,62]; these need further study. The use of oral anticoagulation for the initial 1 to 3 months with or without low-dose aspirin will probably play an increasing role in enhancing further lysis of residual thrombus and minimizing growth of atherosclerotic lesions. Low-dose oral anticoagulation with or without platelet inhibition may play a future long-term role.

Increased attention to risk-factor reduction—especially adjustment of blood lipids (decreasing low-density and increasing high-density lipoprotein cholesterol), control of blood pressure, abstinence from smoking and control of diabetes—is of great importance in reducing the progression of atherosclerotic disease.

REFERENCES

1. Schaper W, Schaper J. Der experimentelle infarkt. *Verh Dtsch Ges Hertz Kreislaufforsch 1979;45:1–6.*

2. DeWood MA, Spores J, Notske R, Mouser LT, Burroughs R, Golden MS, Lang HT. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med 1980;303:897–902.*

3. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, Dodge HT, Francis CK, Hillis D, Ludbrook P. Thrombolysis in myocardial infarction (TIMI) trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. *Circulation 1987;76:142–154.*

4. Chesebro JH, Knatterud G, Braunwald E. Thrombolytic therapy. *N Engl J Med 1988;319:1544–1545.*

5. Verstraete M, Bernard R, Bory M, Brouer RW, Collen D, de Bono DP, Erbel R, Huhmann W, Lennane J. Randomized trial of intravenous recombinant tissue-type plasminogen activator versus intravenous streptokinase in acute myocardial infarction: report from the European Cooperative Study Group for a recombinant tissue-type plasminogen activator. *Lancet 1985;1:842–847.*

6. Anderson JL, Rothbard RL, Hackworthy RA, Sorensen SG, Fitzpatrick PG, Dahl CF, Hagan AD, Browne KF, Symkoviak GP, Menlove RL. Multicenter reperfusion trial of intravenous anisoylated plasminogen streptokinase activator complex (APSAC) in acute myocardial infarction: controlled comparison with intracoronary streptokinase. *JACC 1988;11:1153–1163.*

7. ISIS-2 Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet 1988;2:349–360.*

8. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, or both or neither among 17,187 cases of suspected acute myocardial infarction. ISIS-2. *JACC 1988;12:3A–13A.*

9. Gruppo Italiano per lo Studio della Streptochinasi nell' Infarcto Myocardico (GISSI). Effectiveness of intravenous thrombolytic therapy in acute myocardial infarction. *Lancet 1986;1:397–401.*

10. White HD, Norris RM, Brown MA, Takayama M, Muslowski A, Bass NM, Ormiston JA, Whitlock T. Effect of intravenous streptokinase on left ventricular function and early survival after acute myocardial infarction. *N Engl J Med 1987;317:850–855.*

11. Aims Trial Study Group. Effects of intravenous APSAC on mortality after acute myocardial infarction: preliminary report of a placebo-controlled clinical trial. *Lancet 1988;1:545–549.*

12. Wilcox RG, VonderLippe G, Olsson CG, Jensen G, Skene AM, Hampton JR. For the ASSET Study Group: trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction. *Lancet 1988;2:525–530.*

13. Van der Werf P, Arnold AER. Intravenous tissue plasminogen activator and size of infarct, left ventricular function, and survival in acute myocardial infarction. *Br Med J 1988;297:1374–1379.*

14. Francis CW, Markham RE Jr, Barlow GH, Florack TM, Dobrzynski DM, Marder VJ. Thrombin activity of fibrin thrombi and soluble plasmic derivatives. *J Lab Clin Med 1983;102:220–230.*

15. Fitzgerald DJ, Catella F, Roy L, Fitzgerald GA. Market platelet activation in vivo after intravenous streptokinase in patients with acute myocardial infarction. *Circulation 1988;77:142–150.*

16. Eisenberg PR, Sherman L, Rich M, Schwartz D, Schechtman K, Geltman EM, Sobel BE, Jaffe AS. Importance of continued activation of thrombin reflected by fibrinopeptide A to the efficacy of thrombolysis. *JACC 1986;7:1255–1262.*

17. Lee CD, Mann KG. Activation and inactivation of human factor V by plasmin. *Blood 1989;73:185–190.*

18. Owen J. Friedman KD, Grossman BA, Wilkins C, Berke AD, Powers ER. Thrombolytic therapy with tissue plasminogen activator or streptokinase induces transient thrombin activity. *Blood 1988;72:616–620.*

19. Cercek B, Lew AS, Sato Y, et al. Heparin enhances experimental thrombolysis by preventing new thrombin deposition (abstr). *Circulation 1985;72:suppl III:III-194.*

20. Cercek B, Lew AS, Hod H, Yano J, Reddy NK, Ganz W. Enhancement of thrombolysis with tissue-type plasminogen activator by pretreatment with heparin. *Circulation 1986;74:583–587.*

21. Fitzgerald DJ, Wright F, Fitzgerald GA. Thrombin-mediated platelet activa-

tion during coronary thrombolysis (abstr). *Circulation 1988;78:suppl II:II-120.*
22. Gold HK, Coller BS, Yasuda T, Saito T, Fullon JT, Guerrero JL, Leinbach RC, Ziskind AA, Collen D. Rapid and sustained coronary artery recanalization with combined bolus injection of recombinant tissue-type plasminogen activator and monoclonal antiplatelet GP IIb/IIIa antibody in a canine preparation. *Circulation 1988;77:670–677.*
23. Golino P, Ashton JH, McNatt J, Glas-Greenwalt P, Yao SK, O'Brien RA, Buja LM, Willerson JT. Simultaneous administration of thromboxane A_2—and serotonin S_2—receptor antagonists markedly enhances thrombolysis and prevents or delays reocclusion after tissue-type plasminogen activator in a canine model of coronary thrombosis. *Circulation 1989;79:911–919.*
24. Fuster V, Badimon L, Cohen M, Abrose JA, Badimon JJ, Chesebro JH. Insights into the pathogenesis of acute ischemic syndrome. *Circulation 1988; 77:1213–1220.*
25. Heras M, Chesebro JH, Thompson PL, Fuster V. Prevention of early and late rethrombosis and further strategies after coronary reperfusion. In: Julian D, Kubler W, Norris RM, Swan HJC, Collen D, Verstraete M, eds. Thrombolysis in Cardiovascular Disease. *New York:Marcel Dekker, 1989.*
26. Fuster V, Stein B, Badimon L, Chesebro JH. Antithrombotic therapy after myocardial reperfusion in acute myocardial infarction. *JACC 1988;12:78a–84a.*
27. Badimon L, Lassilla R, Badimon J, Vallabhajosula S, Chesebro JH, Fuster V. Residual thrombus is more thrombogenic than severely damaged vessel wall (abstr). *Circulation 1988;78:suppl II:II-119.*
28. Fesus L, Harsfalvi J, Kovacs E, Muszbek L, Stadler I. Effect of prostaglandin-12 on platelet adhesion. *Biomaterials 1981;2:53–54.*
29. Lam JYT, Chesebro JH, Heras M, Penny WJ, Dewanjee MK, Bailey KR, Badimon L. Deep and superficial arterial injury: Different affinity for thrombus formation at increasing shear rate. *Circulation 1987;76:suppl IV:IV-101.*
30. Lam JYT, Chesebro JH, Steele PM, Badimon L, Fuster V. Is vasospasm related to platelet deposition? Relationship in a porcine preparation of arterial injury in vivo. *Circulation 1987;75:243–248.*
31. Lam JYT, Chesebro JH, Fuster V. Platelets, vasoconstriction and nitroglycerin during arterial wall injury: A new antithrombotic role for an old drug. *Circulation 1988;78:712–716.*
32. Lam JYT, Chesebro JH, Badimon L, Fuster V. Serotonin and thromboxane A_2 receptor blockage decrease vasoconstriction but not platelet deposition after deep arterial injury. *Circulation 1986;74:suppl II:II-97.*
33. Chesebro JH, Smith HC, Holmes DR, Bove AA, Bresnahan DR, Bresnahan JF, Gibbons RJ, Miller FA, Mock MB, Reeder GS, Vlietstra RE, Brown BG. Reocclusion and clot lysis between 90 minutes, 1 day, and 10 days after thrombolytic therapy for myocardial infarction. *Circulation 1985;72:suppl III:III-55.*
34. Nakagawa S, Hanada Y, Koiwaya Y, Taanaka K. Angiographic features in the infarct-related artery after intercoronary eurokinase followed by prolonged anticoagulation. Role of ruptured atheromatous plaque and adherent thrombus in acute myocardial infarction in vivo. *Circulation 1988;78:1335–1344.*
35. Wessler S, Gitel SN. Pharmacology of heparin and warfarin. *JACC 1986;8:10B–20B.*
36. Heras M, Chesebro JH, Penny WJ, Bailey KR, Lam JY, Holmes DR, Roeder GS, Badimon L, Fuster V. Importance of adequate heparin dosage in arterial angioplasty in a porcine model. *Circulation 1988;78:654–660.*
37. Heras M, Chesebro JH, Penny WJ, Bailey KR, Badimon L, Fuster V. Effects of thrombin inhibition on the development of acute platelet-thrombus deposition during angioplasty in pigs: heparin versus recombinant hirudin, a specific thrombin inhibitor. *Circulation 1989;79:657–665.*
38. Lam JYT, Chesebro JH, Badimon L, Fuster V. Serotonin and thromboxane A_2 receptor blockade decreases vasoconstriction but not platelet deposition after deep arterial injury (abstr). *Circulation 1986;74:suppl II:II-97.*
39. Mann KG, Tracy PB, Nesheim ME. Assembly and function of prothrombinase complex on synthetic and natural membranes. In: Oates JA, Harwiger J, Ross R, ed. Interaction of Platelets with the Vessel Wall. *Washington, DC: American Physiologic Society, 1985:47–57.*
40. Topol EJ, George BS, Kereiakes DJ, Stump DC, Candela RJ, Abbottsmith CW, Aronson L, Pickel A, Boswick JM, Lee KL. A randomized control trial of intravenous tissue plasminogen activator and early intravenous heparin in acute myocardial infarction. *Circulation 1989;79:281–286.*
41. Califf RM, Topol EJ, George BS, Boswick JM, Lee KL, Stump D, Dillon J, Abbottsmith C, Candela RJ, Kereiakes DJ. Characteristics and outcome of patients in whom reperfusion with intravenous tissue-type plasminogen activator fails: Results of the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) I trial. *Circulation 1988;77:1090–1099.*
42. Baim DS, Diver DJ, Knatterude GL, TIMI II-A Investigators. "PTCA Salvage" for thrombolytic failures-implications from TIMI IIA (abstr). *Circulation 1988;78:suppl II:II-112.*
43. Topol EJ, Califf RM, George BS, Kereiakes DJ, Rothbaum D, Candela RJ, Abbotsmith CW, Pinkerton CA, Stump DC, Collen D. Coronary arterial thrombolysis with combined infusion of recombinant tissue-type plasminogen activator and urokinase in patients with acute myocardial infarction. *Circulation 1988; 77:1100–1107.*
44. Grines CL, Nissen SE, Booth DC, Branco MC, Gurley JC, Bennett KA, DeMaria AN, and the Kamit Study Group. A new thrombolytic regimen for acute myocardial infarction using combination half-dose tissue-type plasminogen activator with full-dose streptokinase: a pilot study. *JACC 1989;14:573–580.*
45. Badimon L, Badimon JJ, Chesebro JH, Fuster V. Inhibition of thrombus formation: Blockage of adhesive glycoprotein mechanisms versus blockage of the cyclooxygenase pathway (abstr). *JACC 1988;11:30A.*
46. Coller BS. A new murine monoclonal antibody reports an activation-dependent change in the conformation and/or microenvironment of the platelet-GPIIb/IIIa complex. *J Clin Invest 1985;76:101–110.*
47. Gold HK, Coller BS, Yasuda T, Saito T, Fallon JT, Guerrero JL, Leinbach RC, Ziskind AA, Collen D. Rapid and sustained coronary artery recanalization with combined bolus injection of recombinant tissue-type plasminogen activator and monoclonal antiplatelet GPIIb/IIIa antibody in a canine preparation. *Circulation 1988;77:670–677.*
48. Hanson SR, Pareti FI, Ruggeri ZM, Marzec UM, Kunicki TJ, Montgomery RR, Zimmerman TS, Harker LA. Effects of monoclonal antibodies against the platelet glycoprotein IIb/IIIa complex on thrombosis and hemostasis in the baboon. *J Clin Invest 1988;81:149–158.*
49. Torem S, Schneider PA, Hanson SR. Monoclonal antibody-induced inhibition of platelet function: Effects on hemostasis and vascular graft thrombosis in baboons. *J Vasc Surg 1988;7:122–180.*
50. Golino P, Ashton JH, Glas-Greenwalt P, McNatt J, Buja LM, Willerson JT. Mediation of reocclusion by thromboxane A_2 and serotonin after thrombolysis with tissue-type plasminogen activator in a canine preparation of coronary thrombosis. *Circulation 1988;77:678–684.*
51. Guerci AD, Gerstenblith G, Brinker JA, Chandra NC, Gottlieb SO, Bahr RD, Weiss JL, Shapiro EP, Flaherty JT, Bush DE. A randomized trial of intravenous tissue plasminogen activator for acute myocardial infarction with subsequent randomization to elective coronary angioplasty. *N Engl J Med 1987;317:1613–1618.*
52. Kaplan K, Davison R, Parker M, Mayberry B, Feiereisel P, Salinger M. Role of heparin after intravenous thrombolytic therapy for acute myocardial infarction. *Am J Cardiol 1987;59:241–244.*
53. Johns JA, Gold HK, Leinbach RC, Yasuda T, Gimple LW, Werner W, Finkelstein D, Newell J, Ziskind AA, Collen D. Prevention of coronary artery reocclusion and reduction in late coronary artery stenosis after thrombolytic therapy in patients with acute myocardial infarction. A randomized study of maintenance infusion of recombinant human tissue-type plasminogen activator. *Circulation 1988;78:546–556.*
54. The SCATI Group. Randomized control trial of subcutaneous calcium-heparin in acute myocardial infarction. *Lancet 1989;2:182–186.*
55. Bleich SD, Nichols T, Schumacher R, Cooke D, Tate D, Steiner C, Brinkman D. The role of heparin following coronary thrombolysis with tissue plasminogen activator (abstr). *Circulation 1989;80:suppl II:II-113.*
56. Turpie AGG, Robinson JH, Doyle DJ, Mulji AS, Mishkell GJ, Sealey BJ, Cairns JA, Skingley L, Hirsh J, Gent M. Comparison of high-dose with low-dose subcutaneous heparin to prevent left ventricular mural thrombosis in patients with acute transmural anterior myocardial infarction. *N Engl J Med 1989;320:352–357.*
57. Topol EJ, Califf RM, George BS, Kereiakas DJ, Abbottsmith CW, Candela RJ, Lee KL, Pitt B, Stack RS, O'Neill WW, and the Thrombolysis and Angioplasty in Myocardial Infarction Study Group. A randomized trial of immediate versus delayed elective angioplasty after intravenous tissue plasminogen activator in acute myocardial infarction. *N Engl J Med 1987;317:581–588.*
58. Simons ML, Betriu A, Col JL, et al. Thrombolysis with tissue plasminogen activator in acute myocardial infarction: no additional benefit from immediate percutaneous coronary angioplasty. *Lancet 1988;1:197–203.*
59. TIMI Research Group. Immediate versus delayed catheterization and angioplasty following thrombolytic therapy for acute myocardial infarction: TIMI IIA results. *JAMA 1988;260:2849–2858.*
60. Cohen M, Adams PC, Hawkins L, Bach M, Fuster V. Antithrombotic therapy in rest angina prevents death at infarction but not recurrent ischemia (abstr). *Circulation 1989;80:suppl II:II-419.*
61. Wallentin L, RISK Study Group. ASA 75 mg and/or heparin after episode of unstable coronary artery disease—risk for myocardial infarction and death in a randomized placebo-controlled study (abstr). *Circulation 1989;suppl II:II-419.*
62. Badimon L, Badimon J, Lasilla R, Heras M, Chesebro JH, Fuster V. Thrombin inhibition by hirudin decreases platelet thrombus growth on areas of severe vessel wall injury (abstr). *JACC 1989;13:145A.*

Anticoagulant Therapy After Acute Myocardial Infarction

Alexander G.G. Turpie, MD

The use of anticoagulant therapy for patients who have had an acute myocardial infarction is still controversial, mainly because early major studies had conflicting findings, but reanalysis of the data did produce evidence that anticoagulation had clinically and statistically significant benefits. Now more evidence, including the results of a 10-day in-hospital study of low- and high-dose calcium heparin, has been gathered to support using anticoagulants for these patients.

The study used the development of left ventricular mural thrombosis, a frequent complication of acute myocardial infarction that carries a high risk for systmic embolic complications, to assess clinical outcome: A reduced incidence of mural thrombosis would be taken to indicate reduced chances that patients would have major systemic emboli. Two-dimensional echocardiography was used to detect thrombi.

In the study, the incidence of left ventricular mural thrombosis was significantly lower in the high- than in the low-dose group. Among patients in the high-dose group in whom a mural thrombosis did develop, plasma heparin concentrations were significantly lower and activated partial thromboplastin times were shorter. These data suggest that monitoring plasma heparin levels and anticoagulant response can ensure maximal treatment effectiveness. No significant differences in other outcomes—such as bleeding complications, nonhemorrhagic strokes and mortality—were found between the high- and low-dose treatment groups.

(Am J Cardiol 1990;65:20C–23C)

Whether anticoagulant therapy should be administered to patients after an acute myocardial infarction (MI) remains a controversial issue. Accumulating evidence strongly suggests that administering anticoagulant therapy to patients who have had acute MI is associated with several potential benefits. These include: (1) decreasing mortality, (2) reducing infarct extension or recurrent infarction, (3) preventing left ventricular mural thrombosis and systemic embolism, and (4) preventing deep-vein thrombosis and pulmonary embolism. These potential benefits of anticoagulant therapy have not been universally recognized, however, largely because of the conflicting findings of early studies.

The controversy surrounding the use of anticoagulant therapy after acute MI reflects the inconsistent findings of 3 large randomized and controlled clinical trials of anticoagulant therapy for acute MI that were published in the late 1960s and early 1970s.[1–3] All 3 studies reported that anticoagulant therapy resulted in reduced morbidity and fewer systemic emboli and venous thromboemboli. However, only 2 of the studies[1,3] cited fewer strokes or pulmonary emboli. Furthermore, only 1 of the 3 trials[2] showed a statistically significant reduction in mortality. Thus, these findings provided little clear-cut evidence of which outcomes were improved by using anticoagulants.

The results of a subsequent meta-analysis of all trials of anticoagulant therapy for acute MI were published by Chalmers et al[4] in 1977. It provided convincing evidence that anticoagulant therapy does produce a clinically and statistically significant reduction in the major outcomes of MI, including death and thromboembolic events.

However, despite the evidence that anticoagulants are beneficial for treating acute MI, there is currently no consensus on their use. In fact, prescribing patterns vary widely from one region to another. Nowhere is this better illustrated than in the recent International Study of Infarct Survival (ISIS-2) study of the planned use of anticoagulant therapy.[5] This study found that 89% of physicians in France planned to use anticoagulant therapy, compared with no physicians in Belgium. In the United States, use of full-dose intravenous heparin was planned for 37% of patients, oral anticoagulant therapy for 5% of patients, and low-dose subcutaneous heparin for 31% of patients.

There are several reasons why anticoagulant therapy has not been more widely adopted for management of acute MI. These include the inconsistent trial results, the small (although statistically significant) reductions in the major outcomes, and the development of alternative treatment regimens—particularly systemic thrombolytic therapy and early angioplasty.

Moreover, major advances in treating acute MI have

From McMaster University, Hamilton, Ontario, Canada.

Address for reprints: Alexander G. G. Turpie, MD, Hamilton General Hospital, 237 Barton St. E., Hamilton, Ontario L8L2X2, Canada.

been made during the years since the original studies of anticoagulant therapy were conducted, and these advances have resulted in a decrease in control mortality from 20% to only about 10 to 12%. Using today's methodologic standards, many thousands of patients with acute MI would have to be enlisted into a randomized prospective trial in order to demonstrate statistically significant benefits of anticoagulation treatment in reducing major adverse outcomes, such as mortality and systemic embolic events.

LEFT VENTRICULAR MURAL THROMBOSIS AS A "SURROGATE" END POINT

A reasonable alternative study strategy would be to use "surrogates" to assess important clinical outcomes. Left ventricular mural thrombosis is one such possible surrogate. Mural thrombosis is a frequent complication of acute MI. (The frequency of mural thrombosis, as determined by autopsy series, is approximately 50%.) Thrombus formation is probably determined by the interaction of left ventricular systolic dysfunctions, primarily dyskinesia, and endocardial necrosis.

The development of 2-dimensional (2-D) echocardiography has provided an accurate means of detecting thrombi in a clinical setting. Numerous studies of mural thrombosis in patients with acute MI have found the incidence of thrombi to be about 20 to 30% in all patients with MI, but considerably higher (40 to 50%) in patients with anterior transmural MI.

The occurrence of left ventricular mural thrombosis carries a high risk of systemic embolic complications, such as stroke, mesenteric embolism, or acute femoral or brachial artery occlusion. The incidence of systemic embolic events among patients in whom a mural thrombus develops has been reported to be as high as 37%. Although the risk is highest during the first month after an acute MI, thrombi can persist—as can their embolic potential. These embolic events can complicate the care of patients who are convalescing after an acute MI.

Because most clinically significant systemic emboli are associated with left ventricular mural thrombosis, it seems reasonable to consider a reduction in left ventricular mural thrombosis as an indicator for a clinically significant reduction in major systemic embolic events.

METHODS

To explore this hypothesis, a double-blind, randomized multicenter trial was conducted to compare a high vs low dosage of calcium heparin administered subcutaneously for 10 days to prevent left ventricular mural thrombosis in patients with acute anterior transmural infarction.[6] High dosage was defined as 12,500 U every 12 hours; low dosage as 5,000 U every 12 hours.

Study end points: The principal outcome measured by the study was left ventricular mural thrombosis, detected by 2-D echocardiography 10 days after the patient's MI. A positive diagnosis consisted of a well-defined intracavitary mass in contact with, but distinct from, mural endocardium, visualized in more than 1 view or plane, and synchronous in motion with underlying myocardium (Fig. 1). Presence or absence of left ventricular wall motion abnormalities was also noted during echocardiography. Each 2-D echocardiogram was interpreted independently, and in a blinded fashion, by 3 cardiologists who were experienced in the use of echocardiography. Any disagreements were resolved by consensus.

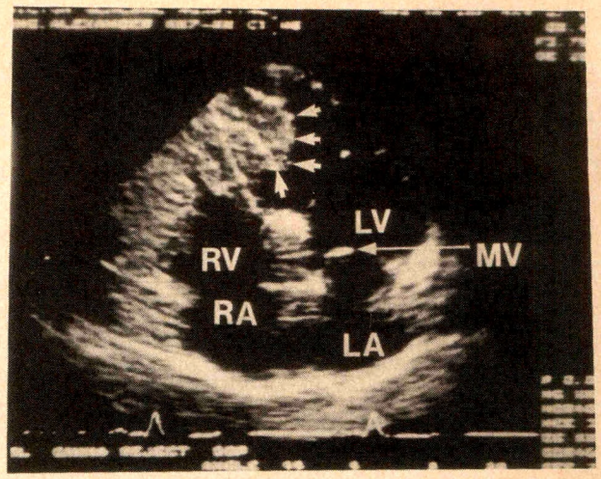


FIGURE 1. Two-dimensional echocardiogram showing a well-defined intracavitary mass in contact with, but distinct from, the mural endocardium. LA = left atrium; LV = left ventricle; MV = mitral valve; RA = right atrium; RV = right ventricle.

Other outcomes assessed by the study included death of the patient, nonhemorrhagic stroke, mesenteric or peripheral arterial embolism, deep vein thrombosis, pulmonary embolism and bleeding complications. All patients were examined daily for evidence of bleeding and other aftereffects during the 10-day treatment period in the hospital, with 2-D echocardiography performed on the tenth day after MI. After discharge from the hospital, the patients were followed for 1 year to keep track of mortality and the development of systemic emboli and venous thromboemboli.

A consecutive series of 233 patients with suspected acute transmural anterior infarction were recruited for the study. Inclusion criteria were (1) typical ischemic pain for at least 20 minutes or longer within 24 hours of assessment, and (2) electrocardiographic evidence of evolving or completed anterior MI.

Patient groups: Patients were excluded if they were age 90 years or older, had undergone cardiopulmonary resuscitation from asystole or secondary ventricular fibrillation, were unable to begin treatment within 36 hours of pain onset, or if heparin administration was contraindicated—e.g., if the patient had active or recent hemorrhage, peptic ulceration or recent surgery.

Of the 233 original patients, 221 were included in analyses of heparin effectiveness and safety (Table I). Of these, 183 (95 in the high-dose heparin group and 88 in the low-dose heparin group) underwent 2-D echocardiography on the tenth day.

There were no significant differences in the baseline characteristics of the patients in the 2 treatment groups. Forty-one percent of the patients had received β blockers, and 19% had received nonsteroidal anti-inflammatory drugs. Only 6% had received aspirin at any time during the first 10 days after infarction. Use of these drugs was

TABLE I Patient Population

Total randomized = 233

Eligible = 221

Ineligible = 12
- No infarction 9
- Major surgery 1
- Refused 1
- Delayed entry 1

2-D echocardiography = 183

No 2-D Echocardiography = 38
- Died <10 days 24
- Refused 8
- Too ill 3
- Technical 3

Rx 36 hours = 171

Rx 36–72 hours = 12

TABLE II Incidence of Left Ventricular Mural Thrombosis at 10 Days After Myocardial Infarction

Finding on 2-D Echo	High-Dose Group	Low-Dose Group
Positive	10 (10.5%)*	28 (31.8%)*
Negative	85	60
Total patients	95	88

* p = 0.00038.
2D Echo = 2-dimensional echocardiography.

TABLE III Creatine Kinase (CK) Concentrations

	CK U/L (mean ± SEM*)
High-dose group	1,097 ± 125
Low-dose group	1,920 ± 149
Positive 2-D echocardiography	2,282 ± 213*
Negative 2-D echocardiography	1,819 ± 108

* p = 0.028
SEM = standard error of the mean.

TABLE IV Plasma Heparin Concentrations and Corresponding APTTs

	High-Dose Group	Low-Dose Group
Mean ± SEM plasma heparin (U/ml)	0.18 ± 0.017	0.01 ± 0.005
Mean APTT (sec)	47.8 ± 1.23	34.8 ± 0.75

APTT = activated partial thromboplastin time; SEM = standard error of the mean.

distributed evenly among the patients in the 2 treatment groups.

RESULTS

The study showed a 10.5% incidence of left ventricular mural thrombosis among the high-dose heparin group, which was significantly lower than the 31.8% incidence among the low-dose group (Table II). Of the 10 mural thrombi in patients who received high-dose heparin, 5 were flat and 5 were protuberant; 1 protuberant thrombus was mobile. Of the 28 mural thrombi in patients treated with low-dose heparin, 15 were flat and 13 were protuberant; none was mobile.

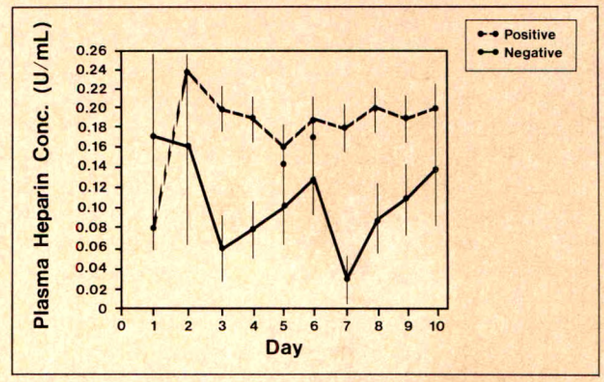


FIGURE 2. Mean plasma heparin concentration in high-dose group: Comparison between patients with positive and negative results on 2-dimensional echocardiography.

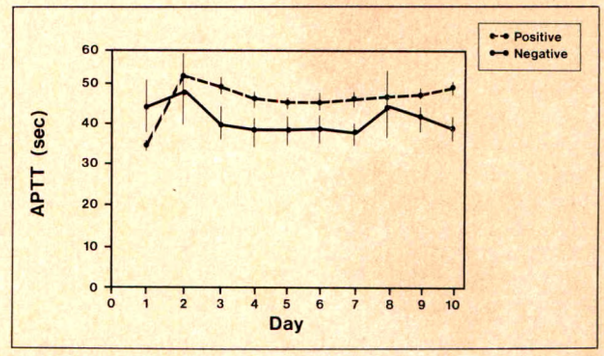


FIGURE 3. Mean activated partial thromboplastin time (APPT) in high-dose group: Comparison between patients with positive and negative results on 2-dimensional echocardiography.

As expected from previous studies, thrombosis and ventricular wall motion abnormalities were associated. Almost 95% of the 183 patients who underwent 2-D echocardiography had abnormal wall motion, which was classified as akinesia in most cases. All patients with mural thrombosis also had wall motion abnormalities, whereas no ventricular thrombi were found in patients with normal wall motion.

Serum creatine kinase levels were measured on hospital admission and again 8 and 16 hours later. The highest concentrations recorded for each patient were used to calculate the mean serum creatine kinase levels. There were no significant differences between the mean creatine kinase concentrations of the high- and low-dose groups.

In contrast, patients with positive results had significantly higher serum creatine kinase levels than patients with negative results on 2-D echocardiograms (Table III). This finding is consistent with the results of previous studies that showed a correlation between the frequency of left ventricular mural thrombosis and infarct size. However, in the high-dose group alone, there were no significant differences in peak creatine kinase concentrations between patients with positive or negative results on 2-D echocardiograms.

Of the 183 patients who underwent echocardiography, 82 were taking β blockers. Of this subgroup, 28% had a mural thrombus, whereas of the 101 patients not receiving β blockers, only 15% had a mural thrombus ($p < 0.01$). The high incidence of mural thrombi in the β-blocking group may be related to the hemodynamic effects of the negative inotropic action of these drugs.

Because all patients were given a constant-dose heparin regimen during the 10-day treatment period, the plasma heparin concentrations and the corresponding activated partial thromboplastin times (APTTs) were measured daily at the midpoint between injections. Not surprisingly, the mean plasma heparin concentration in the high-dose group was significantly higher—almost 20 times higher—than that in the low-dose group. Similarly, the mean APTT in the high-dose group was also significantly higher than that in the low-dose group (Table IV).

In the high-dose group the plasma heparin concentrations were significantly lower among patients in whom a mural thrombus developed than among those in whom it did not. The APTTs were also significantly different: Patients with negative results on the 2-D echocardiogram had longer APTTs (Fig. 2 and 3). These data clearly show the relation between anticoagulant response and clinical effectiveness in preventing left ventricular mural thrombosis. They also suggest that plasma heparin levels and anticoagulant response should be monitored to achieve maximal therapeutic effectiveness.

Other short-term outcomes: During the 10-day in-hospital observation period, there were nonhemorrhagic strokes in 1 of 95 patients in the high-dose heparin group, and in 4 of 88 patients in the low-dose heparin group. This difference was not statistically significant. Four of the 5 patients who had nonhemorrhagic strokes underwent 2-D echocardiography, which showed that 3 of the 4 had a left ventricular mural thrombosis. One patient in the low-dose group had a fatal pulmonary embolism.

There were no cases of transient ischemic attacks or peripheral arterial embolism during the 10-day in-hospital period.

No statistically significant differences were found between the high- and low-dose groups in the frequency of bleeding complications. Overall, 6 patients in the high- and 4 in the low-dose groups had hemorrhagic complications. The only major bleeding complication observed was gastrointestinal hemorrhage, which occurred in 1 patient in each group.

Twenty-four patients died during the 10-day treatment period: 11 in the high- and 13 in the low-dose heparin groups. This difference was not significant. (As was pointed out earlier, mortality was not the primary outcome measured by this study. Thousands of patients would have to be treated and followed in order to detect any significant decrease in mortality.)

Cardiac arrest was the leading cause of death in both groups, but it appeared to occur earlier among patients in the high-dose group. The other causes of death included myocardial rupture, cardiogenic shock and pulmonary embolism—all of which are common causes of mortality among this patient population.

Study follow-up: As mentioned earlier, the patients were observed for up to 1 year after infarction. (The course of therapy after the 10 days of treatment with either high- or low-dose calcium heparin was left to the discretion of the patients' physicians.) Thirty of the 38 patients with positive results on 2-D echocardiograms were treated with anticoagulants for up to 6 months; the remaining patients were treated with antiplatelet agents. In none of the latter did systemic embolism develop during follow-up.

Overall, 4 patients had a stroke during the follow-up period—2 in each of the original treatment groups. In addition, 4 patients—3 in the original high- and 1 in the low-dose groups—had transient ischemic attacks. These cerebral events occurred between the eleventh day and the tenth month after the patient's infarction.

None of these patients had positive results on 2-D echocardiograms or had received anticoagulant therapy after the tenth day.

With regard to long-term mortality, a total of 25 patients died during the follow-up period—13 in the high- and 12 in the low-dose groups. Again, this difference was not significant. One patient in each group died of a stroke, and 1 patient in the low-dose group had a fatal pulmonary embolism 1 month after the acute MI. The deaths of the other 22 patients were due to either documented MI or sudden death.

CONCLUSIONS

The results of this study support the benefits of in-hospital anticoagulant therapy for patients with acute MI. More specifically, this study showed that using high-dose subcutaneous calcium heparin (12,500 U every 12 hours) for patients with acute anterior transmural MI significantly decreased the incidence of left ventricular mural thrombosis. The regimen was not associated with increased incidence of bleeding complications. Furthermore, the beneficial effects of this anticoagulant regimen appear to be related to plasma heparin concentration and to the corresponding APTT response, suggesting that these parameters should be monitored.

Thus, accumulating evidence now strongly supports the wider use of anticoagulant therapy during the immediate post-MI period, to reduce effectively and safely mural thrombosis formation and its potential consequences in terms of morbidity, associated thromboembolic complications and mortality.

REFERENCES

1. Report of the Working Party on Anticoagulant Therapy in Coronary Thrombosis to the Medical Research Council. Assessment of short-term anticoagulant administration after cardiac infarction. *Br Med J 1969;1:335–342.*

2. Drapkin A, Merskey C. Anticoagulant therapy after acute myocardial infarction. *JAMA 1972;22:541–548.*

3. Results of a Cooperative Clinical Trial. Anticoagulants in acute myocardial infarction. *JAMA 1973;225:724–729.*

4. Chalmers TC, Matta RJ, Smith H, Kunzler AM. Evidence favoring the use of anticoagulants in the hospital phase of acute myocardial infarction. *N Engl J Med 1977;297:20:1091–1096.*

5. ISIS-2 Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both or neither, among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet 1988;2:349–360.*

6. Turpie AGG, Robinson JG, Doyle DJ, Mulji AS, Mishkel GJ, Sealey BJ, Cairns JA, Hirsh J, Skingley L, Gent M. Prevention of left ventricular mural thrombosis in acute transmural anterior myocardial infarction: a double blind trial comparing high dose with low dose subcutaneous calcium heparin. *N Engl J Med 1989;320(6):352–357.*

Thromboembolic Complications of Atrial Fibrillation and Their Prevention: A Review

Palle Petersen, MD

Atrial fibrillation (AF) is found in 0.4% of adults younger than age 60 years and in 2 to 4% older than age 60 years, and is associated with a high risk of thromboembolic complications. AF—paroxysmal and chronic—has many etiologies, including rheumatic and nonrheumatic heart disease and thyrotoxicosis. Knowing how strokes occur and what precipitates them—e.g., differentiating between cardioembolic and cerebrovascular causes—is important when deciding on appropriate treatment. Risk factors involved in the development of thromboembolic complications associated with AF are reviewed, focusing on the contributions of thyrotoxic AF, paroxysmal AF (and its transition to chronic AF), enlargement of the left atrium, silent cerebral infarction and decreased cerebral blood flow. Data from several studies are briefly presented, highlighting major outcomes. On the basis of current information about prevention of thromboembolic complications, it seems reasonable to recommend anticoagulant treatment for patients with nonrheumatic chronic AF.

(Am J Cardiol 1990;65:24C–28C)

From the Department of Neurology, University Hospital, Rigshospitalet, Copenhagen, Denmark.

Address for reprints: Palle Petersen, MD, Department of Neurology, University Hospital, Rigshospitalet, DK-2100 Copenhagen, Denmark.

Atrial fibrillation (AF), known to be associated with increased risk of stroke, is found in 0.4% of adults. Its prevalence increases with age, reaching 2 to 4% in persons older than age 60. Cerebrovascular events among patients with AF occur at an overall rate of 25%, with the highest number recorded at onset of AF. In the Framingham study, patients with AF but without rheumatic heart disease had a more than fivefold increase in stroke incidence, whereas patients with AF and rheumatic heart disease had a 17-fold increase, compared with a control population with normal sinus rhythm.

Thromboembolic complications associated with AF cover a wide spectrum, and their manifestation can be either symptomatic or asymptomatic (silent). At one end of the spectrum, stroke is the most obvious symptomatic expression. Transient ischemic attacks, lasting from a few minutes to up to 24 hours, are in the intermediate area. Recent studies suggest that asymptomatic brain infarctions, decreased cerebral blood flow, and perhaps an enlarged atrium, occupy the silent end of the spectrum. In addition, embolism is a well-known complication of electrical cardioversion of AF, occurring in 1 to 3% of patients.

Thromboembolic complications of AF can be caused by paroxysmal atrial fibrillation (PAF) (episodes of short, spontaneous paroxysms) or by chronic AF.

AF can be caused by a number of underlying diseases, including rheumatic and nonrheumatic heart disease (including thyrotoxic heart disease, hypertensive and ischemic heart disease and previous stroke). There is also increased awareness of a group of patients with so-called lone AF, in whom there is no detectable heart disease. The prevalence of lone AF found by various studies has varied from 5 to 25% in patients with PAF and has been about 0.6% in those with chronic AF.

There is a tendency to attribute stroke to cardioembolic sources when AF is present. However, the true incidence of cardioembolic strokes (clinical estimates range from about 20 to 75%) is unknown—unlike strokes related to cerebrovascular disease. Failure to find atrial thrombi by conventional transthoracic echocardiography does not preclude the possibility of cardioembolic stroke. Better results can be obtained with transesophageal echocardiographic methods, particularly with thrombi in the atrial appendage. Other imaging methods, such as computed tomography (CT) scanning, ultrafast CT scanning and nuclear magnetic resonance imaging, may probably also improve detection of atrial thrombi.

Identifying how strokes occur and knowing what pre-

cipitates them have important implications for treating stroke patients and for preventing strokes in others. Such identification would make it possible to define subgroups of patients at high risk of stroke who need aggressive therapy (anticoagulants, aspirin), and subgroups at low risk, who may well need less aggressive therapy directed at specific underlying causes.

THYROTOXICOSIS

Thyrotoxicosis is an important underlying cause of AF. Recent studies have shown a high incidence of cerebral embolism in patients with thyrotoxicosis. Because these trials were not sufficiently controlled, we conducted a retrospective study of a consecutive series of 610 patients with a mean follow-up of 39 months (range 0 to 108). The mean time that elapsed before patients became euthyroid was 10 weeks.[1]

Of the 610 patients, 91 (14.9%) had AF on admission. Frequency increased with age and was >25% after age 60. Only 0.9% of patients younger than age 50 had AF. Sinus rhythm was restored in 46% of patients with AF after treatment for thyrotoxicosis, but the frequency of reversion varied from 100% of the younger patients to 25% of the older. No patient underwent electrical conversion to sinus rhythm.

Cerebrovascular events occurred in 27 patients, 12 in patients with AF and 15 in patients in sinus rhythm. Thirteen events occurred during the first year—5 in patients with AF and 8 in patients in sinus rhythm—and all occurred before the patients became euthyroid. Statistical analysis showed that only age, not gender or AF, was a significant risk factor.

In our study, 13 patients had stroke and 14 had transient ischemic attacks. The risk of stroke with PAF has long been controversial. A recent study of 426 patients with initial PAF found a low frequency of stroke, whereas the stroke rate increased significantly in patients in whom chronic AF later developed.[2] Our study of patients with thyrotoxicosis found no significant difference between PAF and chronic AF in the number of embolic events, indicating that even chronic AF was associated with a low risk of cerebrovascular events. The risk of stroke for patients with thyrotoxic AF thus appears to be lower than previously believed.

Results of our study suggest that patients with AF and untreated thyrotoxicosis do not have significantly more embolic events than age-matched thyrotoxic control patients in sinus rhythm. Nevertheless, the incidence of such events during the first year was slightly higher in the thyrotoxic patients in sinus rhythm, compared with nonthyrotoxic patients in sinus rhythm in epidemiologic studies. Because all cerebrovascular events during this period occurred before the patients became euthyroid, it is recommended that thyrotoxicosis be treated promptly, regardless of electrocardiographic findings.

PAROXYSMAL ATRIAL FIBRILLATION

PAF may play an important role in the development of embolic complications. The only previous study of the risk of embolic complications in patients with PAF showed a rate of cerebral emboli of 6.4% during a 10-year period, but further details on etiologic differences, and on the relation of duration of AF to the incidence of embolism, are unknown.[3]

It is of great clinical importance to know whether PAF carries the same risk of embolic complications as chronic AF. We therefore conducted a retrospective study[2] to relate the rate of systemic embolic complications to underlying etiology, to number of paroxysms, to type of fibrillation (paroxysmal or chronic), and to time of onset of the initial episode.

The study included 426 consecutively hospitalized patients with PAF (median age 66 years; range 20 to 89). Underlying diseases were mainly ischemic or hypertensive heart disease, rheumatic heart disease and thyroid heart disease. Other underlying diseases included cardiomyopathy, lone fibrillation and sick sinus syndrome. No patients received anticoagulant therapy for AF, but patients with established embolic complications received warfarin therapy, if not contraindicated.

The median duration of follow-up for the entire series was 3.5 years (range 0 to 24). Two groups emerged from the retrospective analysis: Group A comprised 285 patients with initial PAF and 1 or more recurrent paroxysms, but without transition to a chronic condition. The median follow-up for this group was 2.9 years (range 0 to 16.2). Group B included 141 patients with initial PAF, 1 or more relapses, and eventual transition to chronic AF. The median follow-up for this group was longer (9 years; range 0 to 24), because their median age at AF onset was lower than the median age of group A (63 vs 68 years).

For 273 patients (64% of the entire series), the initial paroxysm subsided within 1 week, and for 227 patients (53.3% of the series) the duration was less than 1 or 2 days. The initial paroxysmal episode lasted for more than 1 year before spontaneous reversion to sinus rhythm for only 5 patients.

Of the 79 systemic arterial emboli that occurred (18.5% of the entire series), 46 (58.2%) were cerebral. The rate of embolic complications varied significantly with underlying etiologies: They occurred in 15.9% of the patients with nonrheumatic heart disease and in 35.7% of the patients with rheumatic heart disease.

Statistical analysis using Cox's regression model indicated that occurrence of embolic complications was significantly influenced by the transition from PAF to chronic AF, but not by gender, etiology or age. Because the transition to chronic AF depended on etiology (rheumatic heart disease), but not on gender or age, an indirect interaction between etiology and occurrence of embolic complication is implied. Finally, the occurrence of chronic AF also depended on a previous occurrence of embolic complications, whereas mortality rate depended only on embolic complications and age.

During the first 5 years after the initial diagnosis of AF, the overall incidence of embolism with persistent PAF was 6.8% during the first month, decreasing to a rate of about 2% per year for the next 5 years. For pa-

tients who underwent transition of chronic AF, the first-year incidence rate was 13.3%, decreasing to about 4% for the next 4 years.

The yearly mean incidence of emboli during the first 5 years was 2.0% in patients without transition to chronic AF, and 5.1% in patients after transition was established. In both groups, however, distinct clustering of embolic complications occurred during the first year, both at the onset of PAF (65.7%) and at the time of transition to chronic AF (61.3%).

This study confirmed that the risk of stroke is increased for patients with AF due to rheumatic heart disease, compared with other etiologies. However, most of the embolic complications these patients had were seen at the time of or after transition to chronic AF. The 2 etiologic groups with ischemic or hypertensive heart disease did not differ significantly in number of embolic complications.

Of the 141 patients in whom chronic AF eventually developed, 13 had emboli at the time of transition. The incidence of embolic complications from PAF was 2.0%, or about twice the frequency found in epidemiologic studies of patients without AF. The risk of emboli decreased 1 year after the onset of AF, regardless of whether it was chronic or paroxysmal.

Our finding of a 5.1% yearly incidence of embolism associated with chronic AF compared with the 8% found by an earlier cardiac study. Surprisingly, few embolic complications were seen during the course of PAF. Moreover, the finding of very few strokes associated with paroxysmal vs chronic AF cannot be explained by age difference between the groups because the patients with transition were younger than those without.

It is not known why PAF carries a low rate of embolic complications compared with chronic AF. Future studies will have to show whether other factors such as reduced cerebral blood flow and high blood viscosity (e.g., during diuretic treatment of heart failure) contribute to the development of strokes associated with AF. Prophylactic anticoagulation has been advocated on the basis of its effective reduction of embolism in patients with rheumatic AF and with prosthetic valves.

Our findings suggest that further trials of anticoagulation therapy for AF to prevent stroke, particularly for recent-onset AF, appear warranted. More aggressive prophylactic treatment of PAF with antiarrhythmic drugs could possibly postpone the development of chronic AF and thereby reduce the higher risk of embolic complications; however, this approach remains to be ascertained. On the other hand, the possibility of stroke as the initial manifestation of embolism makes the withholding of antithrombotic therapy until embolism is evident an unsatisfactory approach to treatment.

LEFT ATRIAL ENLARGEMENT AND ATRIAL FIBRILLATION

The association of left atrial enlargement with AF is widely accepted, but whether enlargement is a cause or a consequence of arrhythmia is still debated.

To determine left atrial dimensions of patients with AF of short and long duration, we conducted an echocardiographic study involving 3 groups of patients.[4] Group 1 comprised 36 patients (mean age 72 years; range 47 to 87) with AF for less than 3 months, as judged by previous electrocardiograms, careful clinical history and a review of all medical charts and records. Group 2, which comprised 34 patients (mean age 73 years; range 62 to 86) with arrhythmia for at least 1 year, were judged by the same criteria as before. Group 3 was a control group of 31 healthy persons (mean age 73 years; range 58 to 84).

M-mode echocardiography, with the transducer placed in the third intercostal space in the parasternal position, was used to determine left atrial dimension. The anteroposterior dimension of the left atrium was taken as the largest dimension from the leading edge of the posterior aortic wall to the leading edge of the posterior atrial wall. Six months later, all patients with AF again underwent a physical examination, and echocardiography was repeated by the same investigator, without knowledge of the previously measured left atrial dimension.

A highly significant difference in left atrial dimension was found among the 3 groups: The smallest atria (38 ± 6 [mean $\pm$ standard deviation] mm) corresponded to patients in sinus rhythm, the intermediate atria (43 ± 5 mm) to patients with AF of short duration, and the largest atria (49 ± 5 mm) to patients with AF of long duration. When corrected for body surface area, these differences were less pronounced, but remained statistically significant.

When echocardiography was repeated 6 months later, the mean left atrial dimension for short-term AF had increased to 49 ± 6 mm; for long-term AF, it had increased to 53 ± 5 mm. This difference in left atrial dimension between the 2 groups was still significant.

Contrary to some previous studies, our findings of a significant difference between left atrium size in patients with short- and long-term chronic AF, and of a significant increase in size for both groups after 6 months, suggest that AF contributes to the development of atrial enlargement, rather than being caused by it.[5,6] A recent study showed no age or gender influence on left atrial dimension (after correction for body surface area) in an asymptomatic population of 196 patients.[7]

For patients with AF, electrical conversion is the method of choice to restore sinus rhythm. The success of this treatment is related to the duration of the AF, the age of the patient and the degree of left atrium enlargement. The relation found by our study between AF duration and left atrial dimension suggests that considering the size of the left atrium may help in deciding whether to use electrical cardioversion for the AF, especially when its duration is unknown. When AF is associated with clustering of stroke, the implication is that left atrial enlargement has no significance regarding stroke risk as atrial size increases with time; further studies are needed.

SILENT CEREBRAL INFARCTION

The incidence of silent cerebral infarction may be high in patients with AF and cerebral embolism. Using CT scanning, we conducted an investigation to evaluate whether silent cerebral infarction occurs more often in patients with AF without cerebrovascular disease than in

control patients in sinus rhythm. The controlled study matched 30 consecutively chosen patients with electrocardiographic-confirmed AF of more than 1 year's duration, against 30 healthy persons in normal sinus rhythm.[8]

Among the patients with AF, 48% had 1 or more low-density areas visible on the CT scan, compared with 28% of the controls. Although that difference was not statistically significant, the total number of low-density areas was significantly greater in the AF group (n = 39) than in the control group (n = 16). Further analysis of the CT scans showed no difference between the 2 groups in the size of low-density areas. No correlation was found between low-density lesions and age, independent of rhythm disturbance. Similar results have been found by other studies.[9]

The CT scans in our study were evaluated without knowledge of electrocardiographic findings by 2 neuroradiologists not biased in favor of AF or sinus rhythm. Whether the low-density areas found were cerebral infarction or localized atrophy is open to question. Some cerebrovascular events in patients with AF are caused by thrombosis rather than by embolism; and although our controls were healthy, the low-density areas demonstrated by CT scan may reflect thrombotic events caused by atherosclerosis in elderly persons. The higher frequency of lesions found in patients with AF could be explained by cardiac embolization, although echocardiography detected no left atrial thrombi in either group, possibly because of inadequate sensitivity of the echocardiographic method used.

The increased risk of cerebrovascular lesions in patients with AF was expected, but the relatively high incidence of such lesions in healthy persons in sinus rhythm was not. Although some low-density areas identified by our study may indeed represent localized atrophy, we did find more of these areas in patients with AF than in controls, suggesting that for some patients AF leads to localized tissue loss. This finding stresses the need for randomized controlled trials to evaluate thromboembolic prophylaxis for patients with AF.

DECREASED CEREBRAL BLOOD FLOW

Decreased cerebral blood flow may also contribute to the development of cerebrovascular complications in patients with AF. A study was therefore conducted to quantitate reduced cerebral blood flow during AF. This was a small study,[10] comprising 9 patients with AF that had lasted less than 3 months. Cerebral blood flow was measured the day before and the day after electrical cardioversion to sinus rhythm, and again 30 days after conversion.

The day before cardioversion, median cerebral blood flow (expressed as initial slope index) was 36, and the day after, it was 37. After 30 days in sinus rhythm, cerebral blood flow was 39 (not significantly increased), although the end-tidal PCO_2 values were lower than pretreatment values. After correction for changes in end-tidal PCO_2, the median cerebral blood flow had increased significantly, from 36 to 40 on day 1, and to 47 on day 30.

We suggest that the reduced cerebral blood flow that occurs during AF could be a contributing factor to the development of cerebrovascular complications associated with AF. However, larger studies are needed to confirm the findings of this small study.

ORAL ANTICOAGULATION

Administering oral anticoagulants to patients with AF to prevent stroke has been debated for many years. Results of studies of patients with rheumatic AF have suggested that anticoagulants are effective for stroke prevention. A retrospective study of 134 patients with nonrheumatic AF found that the incidence of thromboembolism during periods without anticoagulant therapy was about 8 times greater than during periods with it[11]; however, questions were raised about potential selection bias in determining which patients were to be treated with anticoagulants.

THE COPENHAGEN AFASAK STUDY

To clear up some of these questions, we conducted the Copenhagen AFASAK study,[12] which was a 2-year controlled, randomized study of the effects of anticoagulation with warfarin vs aspirin or placebo in 1,007 patients. There were 335 patients enrolled in the warfarin group, 336 in the aspirin group and 336 in the placebo group.

Patients in the warfarin group were maintained mostly within the therapeutic range: International Normalized Ratio (INR) between 4.2 to 2.8 for 42% of the 2-year treatment time and between 4.2 to 2.4 for 73% of that time. For 0.6% of the time, patients underwent anticoagulation that was too strong (INR above 4.2), and for 26% of the time they underwent inadequate anticoagulation (INR below 2.4). Aspirin was taken once a day (dose 75 mg).

We found that warfarin had a significant effect on prevention of thromboembolic complications in these patients. Five patients taking warfarin had strokes, 4 had disabling cerebral infarction, and 1 had a fatal intracerebral hemorrhage (INR = 3.7). Of the 4 infarcts, only 1 occurred during adequate anticoagulation (INR = 2.9), 1 occurred when treatment was discontinued for evaluation of hematuria (INR = 1.3), and 1 occurred before elective surgery (INR = 1.25). One patient had a stroke before treatment started.

In contrast, aspirin had no significant effect on prevention of thromboembolic complications or vascular death in patients with AF.

In all, 8 patients had fatal strokes: 1 taking warfarin, 3 taking aspirin and 4 taking placebo.

The warfarin group had only 5 embolic complications, and the aspirin and placebo groups had 20 and 21, respectively. There were no embolic complications in the viscera, legs and arms during warfarin treatment, but there were 3 such complications while receiving aspirin and 2 while receiving placebo. The yearly incidence of thromboembolic complications was 2.0% for warfarin, 5.5% for aspirin and 5.5% for placebo.

Adverse effects were more numerous with warfarin (7%) than with aspirin (2%) or placebo (2%). Twenty-one patients taking warfarin were withdrawn from treatment

because of nonfatal bleeding, compared with 2 patients taking aspirin and none taking placebo. However, severe bleeding complications were few.

How long should patients undergo anticoagulation, and should any particular period during AF be considered for anticoagulation? The treatment time for this study was 2 years, so we do not know whether anticoagulation for longer periods is desirable. In contrast to the Framingham study data, we detected no clustering of thromboembolic complications. However, our study design makes it difficult to exclude stroke clustering, because patients with recent-onset AF and stroke were not included.

Further studies on the effect of long-term anticoagulation are still needed, but as long as treatment is not contraindicated, we find it reasonable to recommend anticoagulation therapy with warfarin for patients with chronic nonrheumatic AF.

REFERENCES

1. Petersen P, Hansen JM. Stroke in thyrotoxicosis with atrial fibrillation. *Stroke 1988;19:15–18.*

2. Petersen P, Godtfredsen J. Embolic complications in paroxysmal atrial fibrillation. *Stroke 1986;17:622–626.*

3. Takahashi N, Seki A, Imataka K, Fujii J. Clinical features of paroxysmal atrial fibrillation: An observation of 94 patients. *Jpn Heart J 1981;22:143–149.*

4. Petersen P, Kastrup J, Brinch K, Godtfredsen J, Boysen G. Relation between left atrial dimension and duration of atrial fibrillation. *Am J Cardiol 1987; 60:382–384.*

5. Henry WL, Morganroth J, Pearlman AS, Clark CE, Redwood DR, Itscoitz SB, Epstein SE. Relation between echocardiographically determined left atrial size and atrial fibrillation. *Circulation 1976;53:273–279.*

6. Takahashi N, Imataka K, Seki A, Fujii J. Left atrial enlargement in patients with paroxysmal atrial fibrillation. *Jpn Heart J 1982;23:677–683.*

7. Valdez RS, Motta JA, London E, Martin RP, Haskell WL, Farquhar JW, Popp RL, Horlick L. Evaluation of the echocardiogram as an epidemiologic tool in an asymptomatic population. *Circulation 1979;60:921–929.*

8. Petersen P, Madsen EB, Brun B, Pedersen F, Gyldensted C, Boysen G. Silent cerebral infarction in chronic atrial fibrillation. *Stroke 1987;18:1098–1100.*

9. Kempster PA, Gerraty RP, Gates PC. Asymptomatic cerebral infarction in patients with chronic atrial fibrillation. *Stroke 1988;19:955–957.*

10. Petersen P, Kastrup J, Videbaek R, Boysen G. Cerebral blood flow before and after cardioversion of atrial fibrillation. *J Cereb Blood Flow Metab 1989;9:422–425.*

11. Roy D, Marchand E, Gagné P, Chabot M, Cartier R. Usefulness of anticoagulant therapy in the prevention of embolic complications of atrial fibrillation. *Am Heart J 1986;112:1039–1043.*

12. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomized trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: The Copenhagen AFASAK Study. *Lancet 1989;1:175–179.*

Valvular Heart Disease, Infected Valves and Prosthetic Heart Valves

James E. Dalen, MD

The major causes of systemic embolism from valvular heart disease (mitral, aortic and mitral valve prolapse), prosthetic valves (both mechanical and tissue valves) and infected valves (endocarditis) are reviewed from the standpoint of their incidence and complications. Recommendations for therapy with anticoagulants or other antithrombotic therapy are set forth following the guidelines recently provided by the Second American College of Chest Physicians Conference on Antithrombotic Therapy. Adherence to these recommendations can significantly decrease the risk of systemic embolism in patients with these valvular heart problems.

(Am J Cardiol 1990;65:29C–31C)

From the College of Medicine, University of Arizona, Tucson, Arizona.
Address for reprints: James E. Dalen, MD, Dean, College of Medicine, University of Arizona, 1501 N. Campbell Avenue, Tucson, Arizona 85724.

Accurate diagnosis of systemic embolism, particularly cerebral embolism, was difficult before the introduction of angiography and computerized tomography scanning. The clinical diagnosis of systemic embolism was most often established in patients with valvular heart disease. The occurrence of stroke in young patients with mitral valve disease who did not have risk factors for stroke helped clinicians to recognize that cerebral embolism is a frequent complication of mitral valve disease.

Valvular heart disease used to be the most common cause of systemic embolism because of the high prevalence of rheumatic heart disease. However, as its prevalence has decreased, nonvalvular forms of heart disease have become the major cause of systemic embolism.

In studies of systemic embolism conducted at the Massachusetts General Hospital from 1937 to 1979, the prevalence of rheumatic heart disease among patients with systemic embolism declined from 46% in the period from 1937 to 1953, to 36% from 1954 to 1963, and to 20% from 1964 to 1979.[1]

Cardioembolism, or embolic stroke, comprises about 70% of all systemic embolism. Recent data suggest that rheumatic heart disease is now the source of only 10% of all cases of cardioembolism (Fig. 1).[2] Another 10% of cases are associated with prosthetic heart valves.

SYSTEMIC EMBOLISM IN MITRAL VALVE DISEASE: INCIDENCE AND RISK FACTORS

Systemic embolism in patients with valvular heart disease is seen most often among those who have mitral valve disease. In a number of clinical series of patients with mitral valve disease, about 20% had a history of systemic embolism.[3] At postmortem, the incidence of systemic embolism among patients with mitral valve disease was much higher—40 to 45%.[4]

Several factors may affect the formation of thrombi in the left atrium of patients with mitral valve disease. These are the status of the mitral valve, the patient's age, the presence of atrial fibrillation (AF), and the size of the left atrium.

Coulshed et al,[5] in a review of 839 patients with mitral valve disease, established that the incidence of systemic embolism is nearly the same among patients with rheumatic mitral insufficiency (16%) as among patients with mitral stenosis (19%). The critical factor is AF. In patients with normal sinus rhythm, the incidence of systemic embolism was 8%—both for patients with mitral insufficiency and for those with mitral stenosis. However, when mitral stenosis was complicated by AF, the inci-

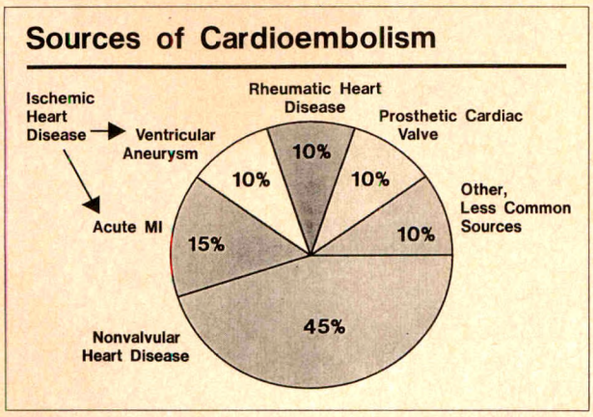


FIGURE 1. Recent data suggest this distribution of sources of cardioembolism. MI = myocardial infarction. (Reprinted with permission from *Chest.*[2])

TABLE I Incidence of Embolism and Hemorrhage in Patients with Tissue Valves Treated with Low-Intensity and Standard-Intensity Warfarin Therapy

	Low Intensity (Mean PT = 16.5 sec)	Standard Intensity (Mean PT = 19.0 sec)	p
Embolism	2/102	2/108	NS
Minor embolism	11/102	11/108	NS
Major hemorrhage	0/102	5/108	<0.05
Minor hemorrhage	6/102	10/108	NS

NS = not significant.

dence of systemic embolism increased to 32%; it was 22% in patients with mitral insufficiency complicated by AF.

Age is an independent risk factor for systemic embolism. Among 737 patients with mitral stenosis and in normal sinus rhythm, the incidence of systemic embolism was 5% for those younger than age 35, but 11% for those older than 35.[5] The size of the left atrium is related to the probability of AF, but by itself does not affect the probability of systemic embolism.[6]

ANTITHROMBOTIC THERAPY IN MITRAL VALVE DISEASE

After reviewing all available studies of thromboembolism among patients with mitral valve disease, the Conference on Antithrombotic Therapy[7] of the American College of Chest Physicians (ACCP) recommended the following therapy[8]:

1. For mitral valve disease complicated by chronic or paroxysmal AF, administer warfarin, adjusted to prolong the prothrombin time (PT) to 1.3 to 1.5 times control, using North American thromboplastin (International Normalized Ratio [INR] = 2.0 to 3.0).

2. For mitral valve disease complicated by systemic embolism, administer warfarin, adjusted to prolong the prothrombin time to 1.5 to 2.0 times control, using North American thromboplastin (INR = 3.0 to 3.5) for 1 year. Then, in the absence of recurrent embolism, decrease the dose to 1.3 to 1.5 times control, using North American thromboplastin.

3. If systemic embolism recurs despite full-dose warfarin (1.5 to 2.0 times control), add dipyridamole 225 to 400 mg/day.

ANTITHROMBOTIC THERAPY IN AORTIC VALVE DISEASE

The incidence of systemic embolism is low in patients with aortic valve disease who do not have associated mitral valve disease or AF. Therefore, antithrombotic therapy is not indicated for these patients.

ANTITHROMBOTIC THERAPY IN MITRAL VALVE PROLAPSE

Mitral valve prolapse may be complicated by transient ischemic attacks (TIAs). However, systemic embolism is rare in the absence of AF or significant mitral regurgitation.

For patients with mitral valve prolapse, the recommendations of the ACCP Conference on Antithrombotic Therapy are as follows[8]:

1. For asymptomatic, uncomplicated mitral valve prolapse, no therapy is required.

2. For patients with a history of TIAs, administer aspirin, 325 mg to 1 g/day.

3. If TIAs recur despite aspirin, administer warfarin (PT = 1.3 to 1.5 times control using North American thromboplastin reagent).

4. For AF or significant mitral regurgitation, administer warfarin (PT = 1.3 to 1.5 times control).

5. For patients with systemic embolism, administer warfarin (PT = 1.5 to 2.0 times control) for 1 year. Then continue warfarin (PT = 1.3 to 1.5 times control).

MITRAL ANULAR CALCIFICATION

Systemic thromboembolism rarely occurs in patients with mitral anular calcification unless it is complicated by AF, mitral stenosis or mitral regurgitation. Antithrombotic therapy is not indicated for this condition unless systemic thromboembolism occurs, in which case warfarin therapy at a PT of 1.5 to 2.0 times control should be given for 1 year, followed by less intense warfarin (PT = 1.3 to 1.5 times control).

If mitral anular calcification is complicated by AF or significant mitral valve disease, warfarin (PT = 1.3 to 1.5 times control) is indicated.[8] Mitral anular calcification may lead to embolization of calcific spicules. However, there is no evidence that antithrombotic therapy prevents this complication.[9]

ANTITHROMBOTIC THERAPY IN PATIENTS WITH PROSTHETIC VALVES

Systemic embolism is the most serious complication of heart valve replacement. Approximately 10% of all systemic emboli occur in patients with prosthetic valves.[2]

The incidence of systemic embolism in patients with mechanical heart valves is sufficiently high to recommend lifelong anticoagulation with warfarin (PT = 1.5 to 2.0 times control, INR = 3.0 to 4.5). Antiplatelet agents

alone do not provide adequate protection. If systemic embolism occurs despite warfarin therapy, dipyridamole, 400 mg/day, should be given in addition to warfarin. If bleeding occurs in patients with mechanical heart valves, one should consider lower-intensity warfarin (PT = 1.3 to 1.5 times control) plus dipyridamole, 400 mg/day.[10]

The incidence of systemic embolism in patients with tissue valves is much lower than that in patients with mechanical heart valves. In the absence of AF, a history of systemic embolism, or a finding of left atrial thrombus at the time of operation, antithrombotic therapy is not indicated for patients with aortic tissue valves.[10]

For patients with tissue valves in the mitral position, less intense warfarin (PT = 1.3 to 1.5 times control) is indicted for 3 months after mitral valve replacement. After 3 months, antithrombotic therapy is not indicated unless AF, a history of systemic embolism, or left atrial thrombus is found at operation.

With these complications, lower-intensity warfarin therapy (PT = 1.3 to 1.5 times control) should be continued.[10] A recent randomized study has shown that less intense warfarin is as effective as the standard intensity (PT = 1.5 to 2.0 times control) in preventing systemic embolism in patients with tissue valves, and it is associated with a much lower incidence of hemorrhage (Table I).[11]

ANTITHROMBOTIC THERAPY IN ENDOCARDITIS

Before the availability of antibiotics, the incidence of systemic emboli among patients with endocarditis was as high as 70 to 90%. Since the introduction of effective antimicrobial therapy, the incidence of emboli has decreased to between 12 and 40%.[8]

Early studies had indicated that anticoagulant therapy did not enhance antibiotic therapy in patients with endocarditis, but did increase the incidence of hemorrhage.[12,13] Some clinicians interpreted these findings to mean that anticoagulants are contraindicated in patients with endocarditis. The more accurate conclusion is that endocarditis, per se, is not an indication for anticoagulant therapy.

For patients with endocarditis who have a mechanical prosthetic valve, anticoagulation with warfarin (PT = 1.5 to 2.0 times control) should be continued to prevent thromboembolism, unless warfarin is contraindicated.[8] For patients who have endocarditis involving a native valve or a bioprosthetic (tissue) valve, but who are in normal sinus rhythm, anticoagulant therapy is not indicated.

If systemic embolism occurs during the course of endocarditis, the decision to use anticoagulation therapy depends on co-morbid factors, because embolism could be due to thromboembolism or to embolization of vegetations.[8] In the latter circumstance, anticoagulant therapy would not be beneficial.

If systemic embolism occurs in a patient with normal sinus rhythm and with endocarditis involving the aortic valve, anticoagulation is not appropriate, especially if vegetations have been noted on echocardiography. At the other extreme, for a patient with endocarditis involving the mitral valve, with AF but without echocardiographic evidence of vegetations, thromboembolism should be assumed; under these circumstances, anticoagulation is appropriate.

CONCLUSION

Patients with mitral valve disease, endocarditis or prosthetic heart valves are at increased risk of systemic embolism. The recent report of the ACCP Conference on Antithrombotic Therapy has reviewed published reports to determine which patients with these disorders should be treated with antithrombotic therapy.[7] Implementation of their recommendations can significantly decrease patients' risk of cerebral and other systemic embolism.

REFERENCES

1. Abbott WM, Maloney RD, McCabe CC, Lee CE, Wirthlin LS. Arterial embolism: a 44-year perspective. *Am J Surg 1982;143:460–464.*

2. Sherman DG, Dyken ML, Fisher M, Harrison MJG, Hart RG. Antithrombotic therapy for cerebrovascular disorders. *Chest 1989;95:suppl 2:140S–155S.*

3. Deverall PB, Olley PM, Smith DR, Watson DA, Whitaker W. Incidence of systemic embolism before and after mitral valvotomy. *Thorax 1968;23:530–536.*

4. Graham GK, Taylor JA, Ellis LB. Studies in mitral stenosis. *Arch Intern Med 1951;88:532–536.*

5. Coulshed N, Epstein EJ, McKendrick CS, Galloway RW, Walker E. Systemic embolism in mitral valve disease. *Br Heart J 1970;32:26–34.*

6. Fleming HA, Bailey SM. Mitral valve disease, systemic embolism and anticoagulants. *Postgrad Med J 1971;47:599–604.*

7. Dalen JE, Hirsh J (eds). Second ACCP Conference on Antithrombotic Therapy. *Chest 1989;66:suppl:1S–168S.*

8. Levine HJ, Pauker SG, Salzman E. Antithrombotic therapy in valvular heart disease. *Chest 1989;95:supl 2:98S–106S.*

9. Fulkerson PK, Beaver BM, Auseon J, Graber HL. Calcification of the mitral annulus: Etiology, clinical associations, complications and therapy. *Am J Med 1979;66:967–977.*

10. Stein PD, Kantrowitz A. Antithrombotic therapy in mechanical and biological prosthetic heart valves and saphenous vein bypass grafts. *Chest 1989;95:suppl 2:107S–117S.*

11. Turpie AGG, Gunstensen J, Hirsh J, Nelson H, Gent M. Randomized comparison of two intensities of oral anticoagulant therapy after tissue valve replacement. *Lancet 1988;1:1242–1245.*

12. Loewe L, Rosenblatt P, Greene HJ, Russel M. Combined penicillin and heparin therapy of subacute bacterial endocarditis. *JAMA 1944;124:144–149.*

13. Thill CJ, Meyer OO. Experiences with penicillin and dicumarol in the treatment of subacute bacterial endocarditis. *Am J Med Sci 1947;213:300–306.*

Cardiac Embolism: The Neurologist's Perspective

David G. Sherman, MD

Cardioembolic stroke represents a major health-care challenge in the United States, accounting for significant morbidity and mortality, as well as economic and social costs. Determining the cause of ischemic stroke is often difficult because multiple potential etiologies are often present and available diagnostic tools are relatively insensitive. The diagnosis of cardioembolic stroke is based on a variety of clinical and laboratory clues that are significant, although not invariable, predictors of stroke etiology. Computed tomography scans help suggest etiology, and scans performed at 48 hours after stroke onset are essential to identify hemorrhagic infarctions. Cerebral angiograms may be helpful if performed early. Echocardiography is indicated only for selected patients who are more likely to demonstrate cardiac abnormalities on an echocardiogram. The management of acute cardioembolic stroke involves weighing the benefits of reducing stroke recurrence by anticoagulation against the risk of symptomatic brain hemorrhage. A management algorithm is provided that can help reduce both the risk of symptomatic brain hemorrhage and the incidence of potentially disabling stroke recurrence.

(Am J Cardiol 1990;65:32C–37C)

From the Department of Medicine-Neurology, University of Texas Health Sciences Center, San Antonio, Texas.

Address for reprints: David G. Sherman, MD, Department of Medicine-Neurology, University of Texas Health Sciences Center, 7703 Floyd Curl Drive, San Antonio, Texas 78284.

Acute stroke has a number of causes. Fifteen percent of patients presenting with an acute vascular disorder have their neurologic deficit as a result of hemorrhage, either intracerebral or subarachnoid. Eighty-five percent of patients with acute stroke have ischemic infarction of the brain.

The major cause of ischemic stroke is large-artery atherosclerotic disease involving the extracranial carotid arteries and the major intracranial vessels. This cause accounts for about 60% of all ischemic strokes. Some 20% of ischemic strokes are caused by small-artery disease, typically affecting the penetrating vessels arising from the middle and posterior cerebral arteries and producing small lacunar infarctions deep within the subcortical white matter and in the basal ganglia. About 15% of strokes have their basis in cardiogenic embolism; these strokes are the focus of this presentation. The remaining 5% of strokes are due to a variety of much less common hematologic and vascular abnormalities.

Cardioembolic stroke is a significant health-care problem in the United States. The most common cause of cardiogenic stroke is nonvalvular atrial fibrillation, accounting for 75,000 strokes annually. Strokes related to emboli after an acute myocardial infarction contribute another 15,000 strokes per year.

Cardioembolic strokes tend to be large and disabling compared with some of the ischemic events occurring as the result of arterial disease. Thus, morbidity, mortality, and cost for acute and chronic care associated with cardioembolic stroke tends to be greater. An estimated $900 million is expended annually on the acute and chronic care of patients with cardioembolic stroke. These facts become especially striking when it is realized that appropriate management, particularly anticoagulation therapy, could possibly prevent many of these strokes.

DIAGNOSIS

The determination of the specific cause of a particular patient's stroke often challenges the clinician's best diagnostic skills.

In police work and the law, when there are no witnesses to a crime, the perpetrator must be identified on the basis of circumstantial evidence. At times, all evidence points to a single perpetrator: A smoking gun is revealed. At other times a number of suspects are capable of having committed the crime, and identifying the guilty party is much more difficult. So, too, with the etiology of stroke: At times all evidence points to a single cause, and you cannot miss the smoking gun; in other cases any one of a number of suspicious factors could have caused the vascular lesion. Unfortunately, that situation is too often the dilemma we face in seeking to detect the cause of a particular stroke.

About 30% of patients with an ischemic stroke have some cardiac abnormality that could have produced their stroke; however, about one-third of these patients also have atherosclerotic disease that could just as likely have been the cause.

There is clearly a tendency to attribute a stroke to the common causes (e.g., large-artery atherosclerotic or small-vessel degenerative disease), and therefore there is frequent underestimation of the incidence of cardiac or other less common causes of ischemic stroke. Thus, in any classification of a large number of patients with ischemic stroke, the number of patients in any category is related to the extent to which the patients have been evaluated, and to the experience and persistence of the evaluators.

There is really no clinical or laboratory "gold standard" for diagnosing cardioembolic stroke. The diagnosis is based on a variety of clinical and laboratory clues. Cardioembolic stroke involves patients of all ages, but its cause is particularly of concern when it involves young patients who are less likely to have atherosclerotic vascular disease.

The onset of a cardioembolic stroke is traditionally described as abrupt and sudden, with the maximal neurologic deficit evident at onset, as opposed to a gradually progressive or stuttering type of onset.

Profile of a cardiogenic embolus: The vascular arterial territory involved in embolic strokes is most often that of the middle or posterior cerebral arteries, or of the top of the basilar artery supplying the posterior cerebral and midbrain region. When the middle cerebral artery is involved, the syndromes of Wernicke's aphasia and of global aphasia without hemiparesis are especially common with an embolic occlusion of a branch of the artery.

The absence of a history of previous transient ischemic attacks (TIAs) in the territory of the stroke is somewhat suggestive of cardioembolic stroke. The absence of a carotid bruit or of peripheral vascular disease is a clue that the patient does not have atherosclerotic vascular disease, and therefore the stroke is somewhat more likely to have a cardiac cause. Certainly, cardiac symptoms surrounding the time of the stroke—palpitations, chest pain or syncope—are suspects for a cardiovascular source. A very high level of suspicion can be placed on the coexistence of a peripheral embolus, which most often is an embolus to an extremity.

Predictors of stroke etiology: Although some specific clinical features suggest cardioembolic stroke, they are by no means invariable predictors of stroke etiology (Table I). Sudden onset of a cerebral deficit is present in 80% of patients with a cardiac cause of their stroke, but it is also present in some 55% of patients with an arterial cause. Loss of consciousness at onset has traditionally been considered more frequent in patients with cardiogenic embolus, occurring in about 19% of such patients, compared with only 3% of patients who have an arterial-cause stroke.

Forty-two percent of patients with arterial causes of stroke have a history of TIAs, but so do 11% of patients with a cardiac-cause stroke. Therefore, a history of TIA is not invariable evidence of an arterial cause. Atherothrombotic strokes are most frequently noted on awakening, but only in about 44% of patients, compared with 26% of patients with cardiac-cause strokes. A stuttering onset of neurologic deficit does not occur often in either type, but occurs slightly more often in patients with arterial causes of stroke, being present in 15% of these patients, compared with 7% of patients with cardiac-cause strokes.

TABLE I Predictors of Stroke Etiology

	Arterial (% of Pts.)	Cardiac (% of Pts.)
Sudden onset	55	80*
LOC at onset	3	19*
TIA history	42*	11
Present on awakening	44*	26
Stuttering onset	15*	7
Carotid stenosis		
≥75%	40*	16
<75%	40	48
Absent	16	24
Systemic embolus	0	100*

* Significantly different.
LOC = loss of consciousness; TIA = transient ischemic attack.

Carotid stenosis due to atherosclerotic disease is more likely to occur in patients with emboli due to an arterial cause. About 40% of all patients with strokes caused by arterial disease have carotid stenoses of 75% or more, and only about 16% have uninvolved carotid arteries. However, even patients with cardiac causes of stroke have carotid stenoses of 75% or more in 16% of cases, and stenoses of less than 75% in 48% of cases.

A systemic embolus is highly predictive of a cardiac source. However, it is a rather infrequent finding, and therefore it is not particularly useful for determining stroke origin.

Radiologic and laboratory findings: Certain radiologic and laboratory features are also useful in diagnosing cardiogenic embolism. The computerized tomography (CT) scan is one of the studies most often obtained for patients with suspected stroke, and it is helpful in suggesting etiology. Patients with cardiogenic embolus are more likely to have cortical distribution of infarcts in the territory of the middle and posterior cerebral arteries. Occasionally, a high-intensity lesion is actually visualized in the area of the middle cerebral artery that represents the embolus. In 10 to 20% of patients with cardiogenic embolus, the CT scan shows a hemorrhagic infarct. However, 90% of patients in whom hemorrhagic infarcts develop have negative CT scans during the first 6 hours after onset. About 80% of patients who will eventually have hemorrhagic infarcts have done so by 48 hours, and the infarcts are visible on CT scans if the scan is recorded at about 48 hours.

Hemorrhagic infarction risk factors include large cerebral infarction and ongoing anticoagulation therapy at the time of onset. It has also been suggested that the presence of early contrast enhancement indicates which patients are likely to undergo hemorrhagic transformation. (Hemorrhagic infarction is discussed at greater length because of its importance in management decisions regarding anticoagulation.)

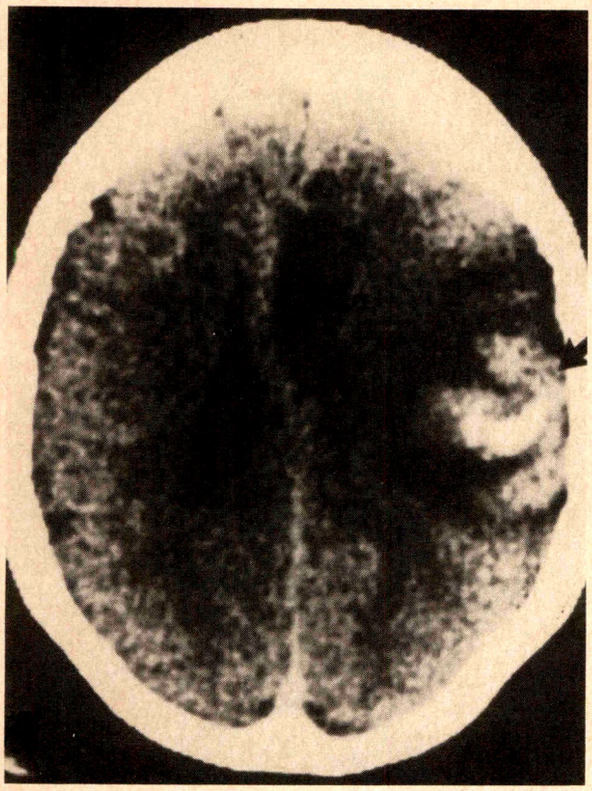


FIGURE 1. This computed tomography scan shows a high-intensity lesion with an irregular border in the territory of the middle cerebral artery.

On a CT scan, a hemorrhagic infarction shows up as a high-intensity lesion with an irregular border (Fig. 1). The presence of such an abnormality on the scan should cause the clinician to suspect the possibility of a cardioembolic stroke.

Cerebral angiography is of some help, permitting several observations. The absence of atherosclerotic vascular disease points away from the most frequent cause of stroke and toward other etiologies. Early in the course of a cardioembolic stroke, it is often possible to see occlusion of branches of the middle or posterior cerebral arteries or occlusion of the most distal portion of the basilar artery (Fig. 2). However, if the angiogram is performed several days after an embolic stroke, or if repeat angiography is performed, no evidence of vascular occlusion may be present because of the lysis and disappearance of the embolic occlusions.

Cardiac studies: What is the role of echocardiography for patients with TIA and stroke? Patients may be thought of as having either a low- or high-yield probability of having a cardiac abnormality seen on echocardiography. For patients who have a low-yield probability, echocrdiography should not be routinely performed. These patients tend to be older than age 60 years and are thus in an atherosclerotic age group. They have no clinical evidence of heart disease by history, physical examination, chest x-ray or electrocardiogram. They have atherothrombotic features in their clinical presentations, CT scans and other laboratory evaluations.

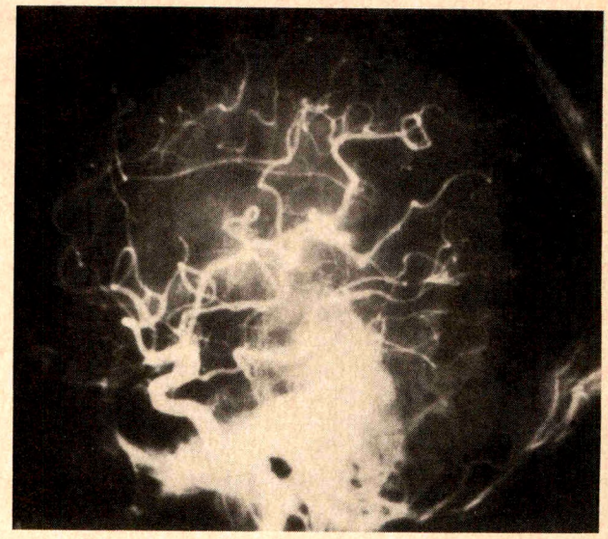


FIGURE 2. The occlusion of a branch in the midportion of the middle cerebral artery territory shown in this cerebral angiogram is typical of what might be seen with a cardiogenic embolus.

Patients with a high-yield probability will show echocardiographic abnormalities in 11 to 25% of cases (Fig. 3). For these patients, echocardiography should be considered necessary to search for a possible cardiac source. The high-yield patients are younger, generally younger than age 50. They have clinical evidence of heart disease by history, physical examination, chest x-ray and electrocardiogram, and they show the features that distinguish the profile of patients with a cardioembolic stroke.

Currently, a number of other diagnostic studies are used or are being investigated for use to identify patients with intracardiac thrombi or with cardiac abnormalities leading to their stroke.

Contrast echocardiography is particularly useful to exclude an interatrial septal defect as the cause of a paradoxic embolus. These patients have a stroke associated with the Valsalva maneuver, and they have peripheral thromboembolic venous disease. Holter monitoring is not particularly helpful, but it will show potentially relevant abnormalities in about 2% of patients. Ultrafast cine cardiac computerized tomography (Fig. 4) is under investigation, and it can show, particularly with views of the left atrium, the presence of thrombi that are otherwise difficult to detect on echocardiography. Magnetic resonance imaging is being evaluated for its role in the detection of intracardiac thrombi, as is transesophageal echocardiography (Fig. 5) and the labeled platelet scintigraphy. The promise of scintigraphy lies in its ability to localize the thrombus within the heart chambers.

To summarize, a reasonable level of suspicion that a stroke has a cardioembolic source is necessary to justify extensive cardiac studies such as echocardiography and Holter monitoring. The yield from these studies will not be rewarding unless the patient has clinical evidence of cardiac disease, or has strong evidence of cardioembolic stroke and no evidence of arterial disease.

Causes of cardiogenic emboli: Almost half of all car-

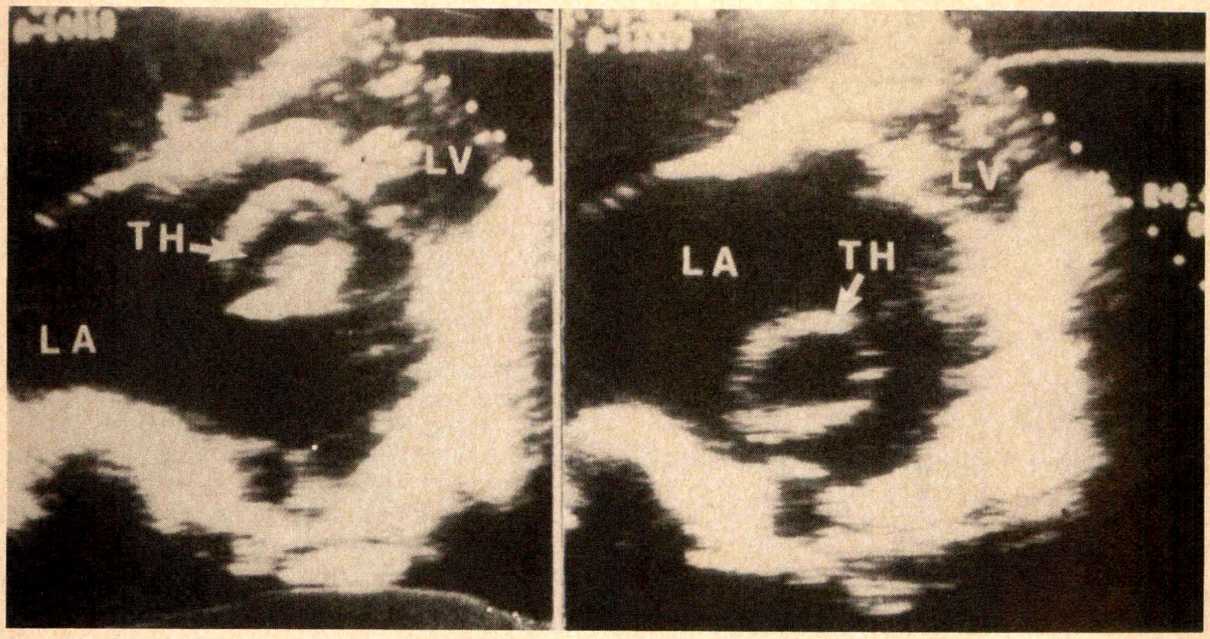


FIGURE 3. These echocardiogram frames show a voluminous thrombus (TH) with a lucent center within an enlarged left atrium (LA). Left atrial thrombi are more often found in the left atrial appendage, which makes them likely to be visualized on an echocardiogram only rarely. LV = left ventricle.

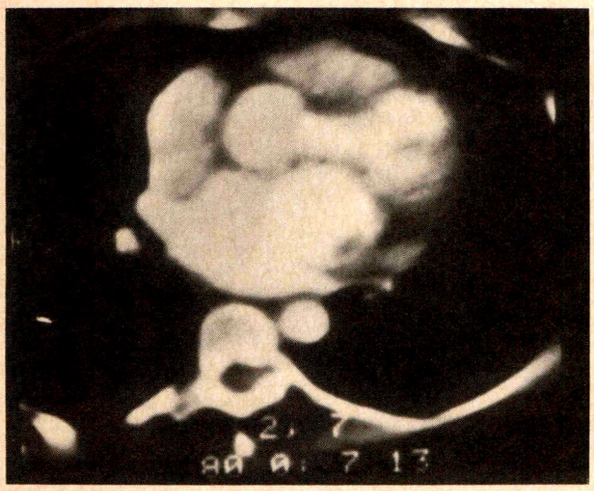


FIGURE 4. This frame from an ultrafast cine computed tomogram shows an enlarged left atrium with a contrast and filling defect that corresponds to a mural thrombus within the left atrium.

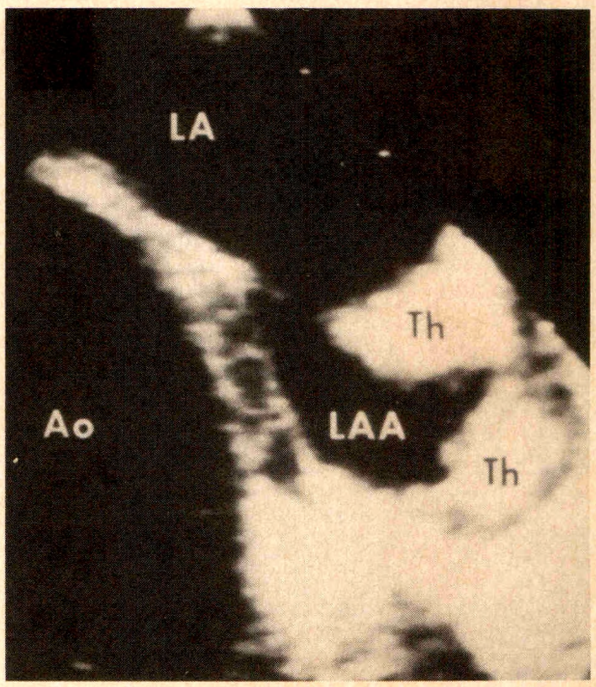


FIGURE 5. Transesophageal echocardiography may facilitate better visualization of thrombi (Th) within the left atrium (LA). Here, it shows 2 discrete thrombi within the left atrial appendage (LAA). Ao = aorta.

diogenic emboli occur in patients with nonvalvular atrial fibrillation (Fig. 6), presumably from thrombi forming within the left atrium and particularly in the left atrial appendage. The risk of embolization in patients with nonvalvular atrial fibrillation is about 5 to 6 times that of a comparable population without atrial fibrillation.

The second most common cause, accounting for 25% of cardioembolic strokes, is ischemic heart disease. Fifteen percent of cases are associated with acute myocardial infarction; most of these are anterior myocardial infarctions with mural thrombus and embolization. Ten percent are associated with ventricular aneurysms and mural thrombi remote from an acute myocardial infarction.

Ten percent of cardiogenic emboli are the result of rheumatic heart disease, generally involving mitral stenosis with atrial fibrillation. Although rheumatic heart dis-

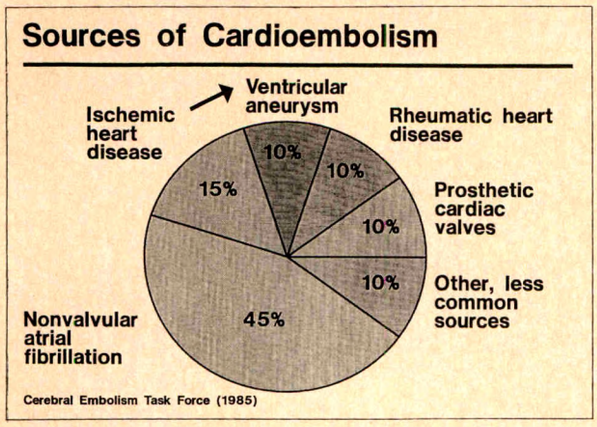


FIGURE 6. Relative frequency of various causes of cardiogenic emboli.

ease has declined as a cause, it still accounts for 1 in 10 cardiogenic emboli.

Another 10% of cardiogenic emboli occur in patients with prosthetic cardiac valves. The remaining 10% are the result of a variety of other cardiac abnormalities, some of which are quite common and are associated with the production of emboli. Other such abnormalities are also quite common, but are rarely associated with the occurrence of emboli.

High-risk patients: A group of cardiac features are generally considered to place patients at high risk for embolism. Anterior myocardial infarction is much more frequently associated with thrombus and embolus than is inferior myocardial infarction. When a patient has left ventricular thrombi, a pedunculated or mobile thrombus is considered much more likely to embolize than a flat, nonmobile thrombus. Congestive heart failure appears to contribute to the development of intracardiac stasis, thrombus formation and embolization. Patients with a prior embolus either to the brain or a systemic vessel have increased risk for a subsequent embolus. Mitral valve stenosis with atrial fibrillation is associated with a risk about 17 times that of a comparable population. Patients with prosthetic mitral valves or infective endocarditis are at fairly high risk of embolization.

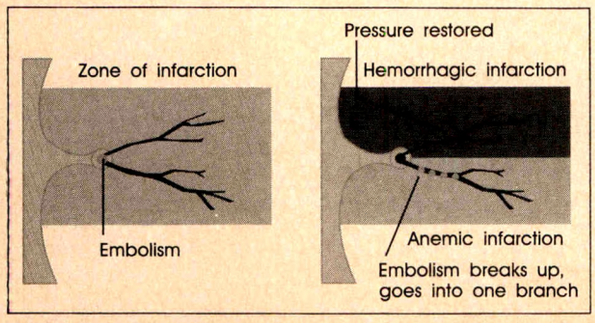


FIGURE 7. The mechanism of hemorrhagic infarction. Physiologic fibrinolysis of an embolic clot permits reperfusion of the region of ischemia and results in leakage of blood into the area of infarction.

Low-risk patients: Cardiac features associated with a low risk of producing an embolism include "lone" atrial fibrillation, (i.e., young patients with paroxysmal atrial fibrillation and no other evidence of organic heart disease), absent or flat thrombus, no congestive heart failure and no prior embolus. Mitral valve prolapse and mitral anulus calcification are disorders that are frequently seen in the general population and in echocardiographic series. Patients must always be investigated for other abnormalities before their stroke is attributed to one of these common disorders.

HEMORRHAGIC INFARCTION

As noted previously, the presence or absence of hemorrhagic infarction, or the exudation of blood into the area of infarction, is highly important in the management decisions regarding anticoagulation. Hemorrhagic infarctions are believed to occur in the following way: An embolus occludes an artery at a bifurcation and produces a zone of ischemia and infarction in the territory supplied by that vessel. The normal fibrinolytic processes of the blood over the course of hours or days cause the embolus to lyse and reopen previously unperfused regions of ischemia. This reperfusion results in leakage of blood into the area of infarction, leading to the production of so-called hemorrhagic infarction (Fig. 7).

Overall, about 20% of cardiogenic brain emboli will become hemorrhagic infarcts. Large strokes tend to have a greater risk for hemorrhagic transformation. Very few patients, if any, have visible hemorrhagic infarction on their CT scans if the scan is performed within the first few hours after stroke onset. About 15% of cases will have evolved into hemorrhagic infarction visible on a scan by 48 hours. If patients are not receiving anticoagulation drugs during this period, they will generally remain asymptomatic despite the oozing of blood into the area of infarction. Although most patients with leakage of blood into the area of infarction will remain asymptomatic, some of them become symptomatic, with large accumulations of blood and formation of hematomas.

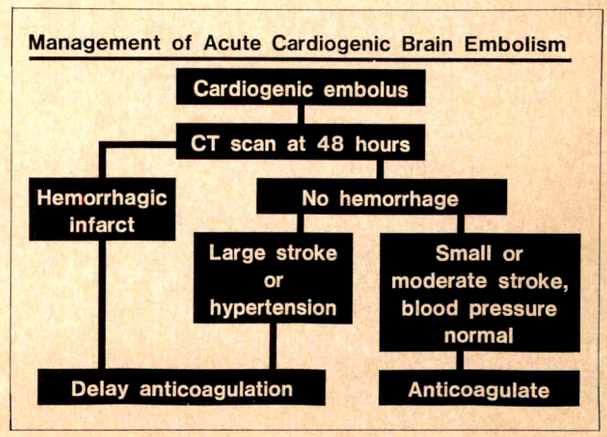


FIGURE 8. An algorithm for the management of acute cardiogenic brain embolism.

TREATMENT

The management dilemma involved in the treatment of patients with acute thromboembolic stroke involves the decision of whether or not to administer anticoagulants. The physician administering anticoagulants to the patient runs the risk of producing a symptomatic hemorrhage and neurologic deterioration. The physician withholding anticoagulation runs the risk that the patient will suffer a recurrent embolic stroke.

The treatment dilemma posed by anticoagulation therapy can be summarized as follows: Without anticoagulation, 12% of patients with a thromboembolic stroke have a recurrent embolism within the first 2 weeks; with it, the recurrence rate is reduced by about two-thirds to 4%. Without anticoagulation, about 1% of patients will have a brain hemorrhage; with it, the incidence of brain hemorrhage is increased to about 5%. Thus, the clinician must balance the reduced risk of recurrence against the increased risk of bleeding.

Identifying patients at the greatest risk of experiencing symptomatic brain hemorrhage as the result of anticoagulation therapy provides the clinician with an important management tool. The patients at greatest risk of brain hemorrhage with anticoagulant therapy appear to be those with large embolic strokes involving, e.g., the entire middle cerebral artery territory. If all these patients are given anticoagulants without having a delayed CT scan performed at approximately 48 hours, there is a risk of including the 10 to 20% of such patients who will undergo spontaneous hemorrhagic transformation and who therefore obviously should *not* be given anticoagulation therapy—and who could be identified by the 48-hour scan.

Persistent hypertension is suggested as a relative contraindication for anticoagulation treatment for acute embolic or thrombotic stroke because the hypertension may worsen any brain hemorrhage that occurs. Patients taking anticoagulation drugs at the onset of their embolic stroke appear to be at increased risk for symptomatic brain hemorrhage if hemorrhagic transformation should occur.

Last, some anecdotal evidence indicates that bolus administration of heparin is more likely to be accompanied by symptomatic brain hemorrhage than is constant infusion.

Patients at low-risk are therefore those with small- to medium-sized strokes, with no evidence of hemorrhagic infarction on a CT scan obtained 48 hours after onset, and with normal blood pressure.

On the basis of these observations, our recommendations for management (Fig. 8) can be summarized as follows: Patients suspected of having a cardioembolic stroke should not be given anticoagulation therapy on the basis of a CT scan performed within the first few hours. Either the initial CT scan should be delayed until 48 hours after onset, or a repeat CT scan should be performed at that time. By then, about 70 to 80% of patients who are destined to undergo hemorrhagic infarction will have done so and can be identified on the CT scan. If at that time the patient is shown to have a hemorrhagic infarction, anticoagulation therapy obviously should be further delayed.

When the 48-hour scan does not show any evidence of hemorrhage, and the patient has only a small- to medium-sized stroke with no problem of blood pressure control, the patient should then be given heparin followed by warfarin. However, if the patient has a large stroke or persistently elevated blood pressure, anticoagulation treatment should be further delayed for at least 7 to 10 days because of the high risk that these particular patients may undergo symptomatic brain hemorrhage.

SUMMARY

Cardioembolic strokes are significant contributors to stroke morbidity and mortality, and cardioembolism is probably underestimated as to its frequency and importance as a cause of stroke. There is often considerable ambiguity in determining whether a patient indeed has a cardioembolic stroke. Many of the tools that we use are relatively nonspecific and insensitive, and there is a tendency for multiple potential etiologies to be present.

Management of acute cardioembolic stroke is based on weighing the benefits of reducing stroke recurrence of anticoagulation therapy against the risks of symptomatic brain hemorrhage if the patient is given anticoagulants. Delaying or eliminating anticoagulation for patients who appear to be at particularly increased risk (i.e., patients with large strokes or hemorrhagic infarction on delayed CT scan), and providing anticoagulation to other patients, may reduce both the risk of symptomatic brain hemorrhage and the incidence of potentially disabling cardioembolic stroke recurrence.

Antithrombotic Therapy in Cardiac Disease: An Approach Based on Pathogenesis and Risk Stratification

Valentin Fuster, MD, Bernardo Stein, MD, Jonathan L. Halperin, MD, and James H. Chesebro, MD

An approach to the management of thrombosis and embolism in various cardiovascular disorders is discussed. This approach is based on current knowledge of pathogenesis and risk of thromboembolism. Rational therapeutic guidelines are formulated along the lines of anatomic location (arterial circulation, cardiac chambers or prosthetic valves), pathophysiology (activation of platelets or the coagulation system, or both), and degree of thromboembolic risk. With clear understanding of these factors, it may be possible to determine the most suitable platelet inhibitor or anticoagulant regimen for the individual patient, and whether these agents should be given singly or in combination.

(Am J Cardiol 1990;65:38C–44C)

From the Mount Sinai School of Medicine, New York, New York, and the Mayo Clinic, Rochester, Minnesota.

Address for reprints: Valentin Fuster, Mount Sinai Medical Center, Division of Cardiology, Box 1030, One Gustave L. Levy Place, New York, New York 10029.

Parts of this study appeared in: Stein B, Fuster V, Halperin JL, Chesebro JH. Antithrombotic therapy in cardiac disease: an emerging approach based on pathogenesis and risk. *Circulation 1989;80:1501–1513; with permission from the American Heart Association, Inc.*.

Thrombosis and embolism are among the most important contributors to cardiovascular morbidity and mortality. A rational approach to this problem is derived from understanding the pathophysiologic mechanisms underlying thromboembolism in the arterial circulation, cardiac chambers and valves, as well as from the identification of different risk categories. In this review we will briefly discuss: (1) mechanisms of thrombosis and embolism, (2) risk stratification, and (3) proposed antithrombotic approach based on pathogenesis and risk.

MECHANISMS OF THROMBOSIS AND EMBOLISM

Arterial circulation: When superficial injury to the vessel wall occurs, only a monolayer of platelets adheres to the damaged endothelium or exposed subendothelium.[1] When arterial injury is more severe—as in cases of atherosclerotic plaque rupture or during angioplasty—components of the arterial media, including collagen, become exposed to the circulating blood. This results in marked activation of platelets, which occurs predominantly by way of 3 metabolic pathways. In the first pathway, collagen (derived from the damaged vessel wall) and thrombin (produced during activation of the coagulation cascade) stimulate the release of intracytoplasmic calcium, resulting in platelet contraction. This leads to a change in the configuration of the platelet membrane receptor (the glycoprotein IIb/IIIa), with exposure of the binding sites for fibrinogen and von Willebrand factor. These 2 molecules are essential for the process of platelet aggregation (Fig. 1). In addition, platelet contraction results in the release of adenosine diphosphate and serotonin from intracytoplasmic granules, which stimulate neighboring platelets and promote aggregation (second pathway). Furthermore, calcium also results in the release of arachidonic acid from the platelet membrane, with the subsequent formation of thromboxane A_2, which is a potent platelet aggregator (third pathway) and vasoconstrictor.

As mentioned, deep vessel wall damage results not only in the exposure of collagen, but also stimulates the formation of thrombin through the intrinsic (surface-activated) and extrinsic (tissue factor-dependent) coagulation pathways, in which the platelet membrane favors the interaction between clotting factors. Thrombin promotes the formation and stabilization of fibrin, and is a powerful activator of platelet aggregation. Therefore,

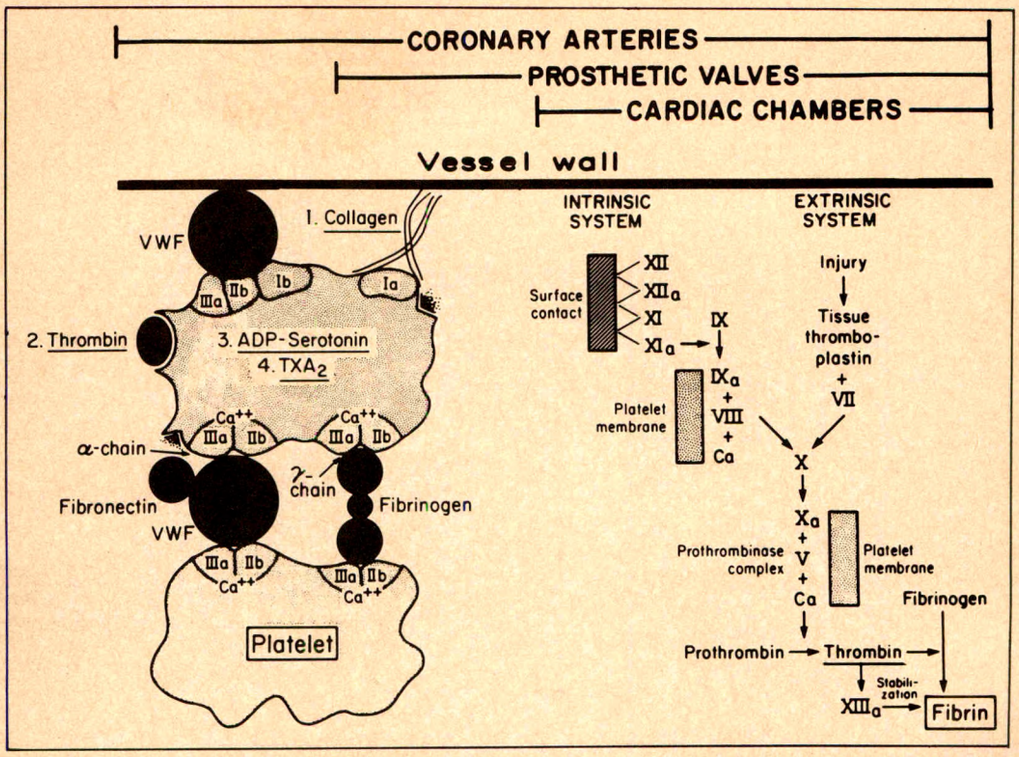


FIGURE 1. ***Left,*** **biochemical interactions between platelet membrane receptors (glycoproteins Ia, Ib and IIb/IIIa), adhesive macromolecules and the vessel wall during thrombogenesis. The pathways of platelet aggregation dependent on collagen, thrombin, adenosine diphosphate (ADP)–serotonin, and thromboxane A_2 (TXA_2) are depicted.** ***Right,*** **intrinsic and extrinsic pathways of the coagulation system with the generation of thrombin and fibrin. Note that thrombosis in coronary arteries involves both platelet and coagulation factors. Prosthetic valves activate the clotting system primarily, and platelets, secondarily. Cardiac chamber thrombosis involves clotting activation. Ca = calcium; VWF = von Willebrand factor. (Modified with permission from: Stein B, Fuster V. Antithrombotic therapy in acute myocardial infarction: prevention of venous, left ventricular and coronary artery thromboembolism.** ***Am J Cardiol 1989;64:33B–40B*****).**

platelets and the coagulation system are clearly interrelated in the genesis of arterial thrombosis (Fig. 1).

Perfusion chamber experiments[2] have analyzed the influence of wall shear rate and degree of vascular damage on platelet/thrombus formation. These studies suggested that, with superficial vessel injury, platelet deposition increased proportionally to the shear rate, but the phenomenon was only transient. In contrast, with deep vessel injury, platelet deposition was enhanced and could lead to persistent vascular thrombotic occlusion. These concepts are important in the pathogenesis of acute coronary syndromes. In unstable angina, plaque fissuring may lead to transient vessel occlusion due to an evanescent thrombus; the duration of vascular occlusion is short and does not result in myocardial necrosis. In myocardial infarction, more severe arterial wall injury may lead to persistent thrombotic occlusion and myocardial necrosis. The presence of a thrombus or residual stenosis after spontaneous or pharmacologic thrombolysis and after angioplasty predisposes to acute vessel thrombosis and reocclusion.

Cardiac chambers: The pathogenesis of intracavitary thrombosis may be outlined along the lines established by the pathologist Virchow in the previous century, who described a triad of precipitating factors: endothelial injury, circulatory stasis and hypercoagulability. Endocardial injury has been identified in patients in the first days after myocardial infarction, and in those with left ventricular aneurysm or dilated cardiomyopathy. This injury exposes the subendothelial tissue to the circulating blood, promoting thrombosis.

The presence of blood stasis in hypokinetic or dyskinetic areas promotes the development of left ventricular mural thrombi. In addition, blood stasis contributes to the formation of atrial thrombi in cases of impaired atrial mechanical activity, as occurs in atrial fibrillation, mitral stenosis and heart failure. Blood stasis, characteristic of conditions of low shear rate, leads to activation of the coagulation system rather than of platelets and constitutes the predominant mechanism in the pathogenesis of intracavitary thrombi. In addition, the presence of a hypercoagulable state, as may occur after acute myocardial infarction, may contribute to thromboembolism.

While the aforementioned factors—injury, stasis and hypercoagulability—predispose to thrombosis, the migration of thrombotic material is dependent on the dynamic forces of the circulation.[3] Therefore, even though stasis favors thrombosis within the sac of a left ventricular aneurysm, isolation from the circulation protects against embolism.[4] In contrast, in acute myocardial infarction

TABLE I Emerging Antithrombotic Approach to Cardiac Disease Based on Pathogenesis and Thromboembolic Risk

	Thromboembolic Risk		
	High (>6%/year)	Medium (2–6%/year)	Low (<2%/year)
Arterial system	Unstable angina Acute MI MI–after thrombolysis PTCA—early phase SVBG—early phase	Chronic stable angina Chronic phase after MI PTCA—chronic phase SVBG—chronic phase	Primary prevention of cardiovascular disease
Platelets + fibrin	Platelet inhibitor plus anticoagulant*	Platelet inhibitor or anticoagulant (INR 2.0–3.0)†	Platelet inhibitor‡
Cardiac chambers	AF—prior embolism AF—mitral stenosis	AF—other forms of organic heart disease Early phase after anterior MI Dilated cardiomyopathy	AF—idiopathic Chronic LV aneurysm
Fibrin	Anticoagulant (INR 3.0–4.5 in prior embolism, or 2.0–3.0 in mitral stenosis)	Anticoagulant (INR 2.0–3.0)	Usually no need for therapy
Prosthetic valves	Old mechanical prostheses Mechanical protheses—prior embolism	Recent mechanical prostheses Bioprotheses—AF	Bioprostheses—normal sinus rhythm
Fibrin + platelets	Anticoagulant (INR 3.0–4.5) plus platelet inhibitor	Anticoagulant (INR 3.0–4.5) in mechanical prostheses, or 2.3–3.0 in bioprostheses	Usually no need for therapy

* Heparin may be used in the acute phase (activated thromboplastin time: 1.5 to 2.0 × control); its use in combination with aspirin is evolving in patients at high risk.
† Although both are beneficial, platelet inhibitor therapy is recommended based on lower toxicity, cost, and ease of administration.
‡ Recommended for persons at high risk for coronary disease.
AF = atrial fibrillation; INR = International Normalized Ratio of prothrombin suppression; LV = left ventricular; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; SVBG = saphenous vein bypass graft.

and dilated cardiomyopathy, the resulting mural thrombus is in contact with the circulating blood, and may be propelled into the ventricular outflow tract, leading to embolism. This apparent paradox should be taken into consideration in the appropriate management of these patients.

Prosthetic valves: Mechanical prostheses are significantly more thrombogenic than their biologic counterparts. The prosthetic surface area exposed to the circulation (including the endocardium-suture-prosthesis interfaces) is the major factor leading not only to platelet activation but, more important, to activation of the coagulation cascade.[5] Flow stasis and abnormal hemodynamic characteristics of the prosthetic devices mainly promote fibrin formation and promote platelet aggregation secondarily.

Biologic prostheses are less thrombogenic because of the natural properties of the material used in their construction and because of leaflet pliability, axial flow profile and cyclic sinusoidal washout.[6]

In summary, arterial thrombosis involves vessel wall damage and exposure of a thrombogenic substrate, resulting in activation of both platelets and the coagulation system. Intracavitary thrombosis occurs predominantly in situations of circulatory stasis, which favor activation of the coagulation cascade and fibrin formation. Finally, mechanical prostheses primarily lead to activation of the clotting system and, secondarily, to activation of platelets, whereas bioprostheses are considerably less thrombogenic.

STRATIFICATION OF THROMBOEMBOLIC RISK

The pathogenesis and anatomic location of a thromboembolic process dictates the type of antithrombotic therapy best suited for a particular patient. The intensity of therapy, however, is also dependent on the individual's risk of thrombosis and embolism. In the high-risk category are patients with a predicted incidence of thromboembolism of more than 6% per year. At medium risk are those with an incidence of thromboembolism that ranges from 2 to 6 per 100 patients/years. Finally, the low-risk group includes those with fewer than 2 episodes per 100 patients/year (Table I).

For thrombosis within the *arterial circulation*, 3 risk groups are identified: Patients at high risk are those with unstable angina, acute myocardial infarction, after thrombolysis for acute infarction, and during the early phase of both transluminal coronary angioplasty and saphenous vein graft bypass surgery. In the medium-risk category are patients with stable angina pectoris and those in the chronic phase after myocardial infarction,

coronary angioplasty and bypass surgery. When antithrombotic therapy is considered for primary prevention of coronary disease, these patients are included in the low-risk group, because their thrombotic risk is below 1% per year.

With regard to *cardiac chamber* thrombosis and embolism, patients at highest risk are those with atrial fibrillation and prior embolism (within the preceding 2 years). At somewhat lower but still substantial risk, are those with atrial fibrillation and mitral stenosis and those with uncontrolled hyperthyroidism. At medium risk are patients with atrial fibrillation and other forms of organic heart disease: hypertensive, ischemic, cardiomyopathic and valvular (excluding mitral stenosis). Patients in the early phase after anterior infarction and those with dilated cardiomyopathy are also at medium risk for thromboembolism. At lowest risk are patients with idiopathic (lone) atrial fibrillation and those with chronic left ventricular aneurysm (more than 3 months after myocardial infarction).

In patients with valvular prostheses, those with old mechanical prostheses (implanted before the mid-1970s) and those with prior embolism are at highest risk. At medium risk are patients with modern mechanical prostheses and those with bioprostheses in the presence of atrial fibrillation. At lowest risk are patients with bioprostheses along with normal sinus rhythm.

ANTITHROMBOTIC TREATMENT BASED ON PATHOGENESIS AND RISK

With the foundations established in the sections of pathogenesis and risk stratification, a rational approach to the selection of antithrombotic agents is outlined in Table I. The numerical values correspond to the high-, medium- and low-risk clinical situations and should be taken only as flexible and approximate values, since distinguishing patient characteristics preclude rigidly defined categories. Therapeutic recommendations are formulated along the lines of anatomic location and pathogenesis, represented by the horizontal rows in the table. In general, for patients at high risk, aggressive antithrombotic therapy is recommended. In contrast, for patients at low risk, antithrombotic therapy may not even be necessary. For the medium-risk group, an intermediate approach is suggested.

Arterial circulation: Injury to the vessel wall leads to activation of platelets and of the coagulation system, with the production of thrombin and fibrin; the particular clinical situation will dictate whether a platelet inhibitor, an anticoagulant, or the combination of both is indicated. The patient's risk of thrombosis will determine the intensity of therapy.

High risk: Patients with unstable angina are at increased risk of infarction and cardiovascular death. Several randomized trials have clearly demonstrated that platelet inhibitor therapy with aspirin[7–9] or with ticlopidine[10] reduces the incidence of myocardial infarction and death. In addition, the findings of 2 other studies[9,11] support the use of heparin during the acute stage. In 1 trial,[9] aspirin, heparin, and the combination of both were found effective, with a trend favoring heparin over aspirin. Because in some patients with unstable angina, myocardial infarction develops despite treatment with 1 agent or the other, the combination of low-dose aspirin (80 mg/day) and heparin (activated thromboplastin time 1.5 to 2.0 × control) may be more effective and needs to be tested in larger clinical trials. Beyond the acute phase, a daily dose of 325 mg of aspirin is recommended.

The value of aspirin in the acute phase of myocardial infarction was substantiated by the results of the Second International Study of Infarct Survival (ISIS-2) trial.[12] Aspirin, which probably acts by preventing reinfarction after spontaneous or pharmacologic thrombolysis, significantly reduced vascular mortality and reinfarction when used alone or in combination with streptokinase. The issue of short-term anticoagulation in acute myocardial infarction for the prevention of reinfarction and mortality is still unsettled. Although large studies showed that anticoagulant use was associated with a trend toward lower reinfarction, only when the results of randomized trials were pooled[13] was a significant reduction in mortality seen (20%). Because of the high risk of reinfarction and death in the first weeks after acute myocardial infarction, the combination of aspirin and an anticoagulant may prove beneficial and deserves clinical testing.

Based on the results of the ISIS-2 trial, with regard to anticoagulants, a recent Italian multicenter trial (SCATI)[14] showed that subcutaneous heparin (12,500 units twice daily) reduced mortality in patients with acute myocardial infarction treated with intravenous streptokinase. Thus, a beneficial role for aspirin[12] or for heparin[14] as adjunctive therapy to thrombolysis is supported by recent clinical trials. Patients with acute infarction treated with thrombolytic agents should receive aspirin on admission.[12]

Substantial damage to the vessel wall during coronary angioplasty predisposes to acute thrombotic vessel occlusion. Several studies[15–17] have clearly shown that pretreatment with aspirin, aspirin plus dipyridamole, or ticlopidine significantly reduces the incidence of coronary occlusion and infarction during and after angioplasty. The role of heparin has not been properly tested in clinical trials; however, experimental data showed an inverse relation between heparin dose, platelet deposition and thrombosis.[18] Given the propensity for acute thrombotic complications during angioplasty, pretreatment with aspirin combined with adequate heparinization throughout the procedure is clearly indicated. Aspirin taken daily is recommended after discharge.

Coronary artery bypass surgery can be complicated by early graft occlusion that is mainly thrombotic in origin and in which platelets play a major pathogenic role. Several trials[19–21] have documented that aspirin, with or without dipyridamole, or ticlopidine reduces the incidence of graft occlusion when given preoperatively or soon after operation. Because preoperative aspirin increases the risk of postoperative bleeding, we prescribe dipyridamole preoperatively, followed by aspirin (325 mg/day) alone, starting in the immediate postoperative period. In addition to antiplatelet therapy, intraoperative

heparin is necessary for prevention of thrombosis in this high-risk population. Beyond the acute phase, patients are at risk of recurrent coronary thrombosis and vein graft closure. Therefore, long-term aspirin therapy appears sensible.

Medium risk: Patients with stable angina are often treated empirically with platelet inhibitor therapy. Preliminary evidence[22] from a randomized, angiographic trial in patients with stable coronary disease suggests that antiplatelet therapy reduces the incidence of myocardial infarction and new lesion formation; however, it does not prevent the progression of disease in patients with preexisting lesions.

In survivors of myocardial infarction, the search for an effective antithrombotic regimen for the prevention of reinfarction and mortality has generated enormous controversy. Even though at least 10 trials of antiplatelet therapy have been reported, no single trial has succeeded in providing a definitive answer; however, when all the trials are pooled,[23] antiplatelet treatment reduces the incidence of cardiovascular events by 25%. Aspirin alone is as effective as it is in combination with dipyridamole and more effective than sulfinpyrazone. Therefore, aspirin, 325 mg/day, is recommended to survivors of myocardial infarction.

The use of postinfarction anticoagulant therapy has yielded conflicting results. Most large studies show a trend toward lower reinfarction, but the effects on mortality are less evident. One randomized trial[24] assigned patients who had undergone anticoagulation (6 years after infarction) to continue the anticoagulant or substitute placebo. After 2 years, those who continued to receive warfarin therapy had a significant reduction in reinfarction and lower mortality. Furthermore, preliminary evidence from the Norwegian (WARIS) trial[25] strongly supports the use of warfarin after infarction, for the prevention of reinfarction and death. Therefore, for the secondary prevention of postinfarction cardiovascular morbidity and mortality, available evidence supports the use of either aspirin or an anticoagulant. At a dose of 325 mg/day, aspirin offers several advantages over long-term anticoagulation, in terms of cost, ease of administration and safety.

Low risk: Given the prevalence of coronary disease in our society, attempts at primary prevention of myocardial infarction and cardiovascular death are warranted. Two primary prevention trials were recently published.[26,27] The United States trial[26] showed that aspirin (325 mg administered every other day) reduced the incidence of myocardial infarction by almost 50%, while the smaller, British study [27] found no benefit from 500 mg of aspirin a day. Neither study found a reduction in overall mortality, but aspirin was associated with a slight increase in the risk of hemorrhagic stroke. When both studies are analyzed together, aspirin is seen to exert a beneficial effect by reducing the incidence of myocardial infarction, at the price of a slightly increased risk of brain hemorrhage. Aspirin appears to have a greater beneficial impact in patients with risk factors for coronary disease[26] and in those with evidence of cerebral or peripheral artery disease. Therefore, one may recommend aspirin to male patients older than age 40 years, who have risk factors for coronary disease or evidence of disease in other vascular territories. In addition, the control of risk factors in these patients is of primary importance.

In summary, thrombosis within the arterial system involves both platelet and clotting activation. For patients at high risk, the combination of a platelet inhibitor and an anticoagulant (in the acute phase) should be considered. For those at medium risk, either a platelet inhibitor or an anticoagulant is beneficial, although the former is favored because of lower toxicity and cost. Finally, for those at low risk, a platelet inhibitor can be recommended to selected patients (Table I).

Cardiac chambers: Thrombosis within the left atrium and left ventricle is primarily due to blood stasis, which results in activation of the coagulation system rather than of platelets. Therefore, anticoagulant agents are essential to the management of most of these patients, except for those at lowest risk (Table I).

High risk: Patients at highest risk are those with a history of systemic embolism over the previous 2 years. Although no prospective randomized trials using anticoagulants are available, the marked increase in risk warrants the use of anticoagulant therapy aimed at prolonging the prothrombin time (PT) to 1.5 to 2.0 × control (International Normalized Ratio [INR] of prothrombin suppression, 3.0 to 4.5). Also at significant embolic risk are patients with atrial fibrillation and mitral stenosis. Several nonrandomized trials have shown that anticoagulant therapy reduces the incidence of embolism by 25%.[28] These patients should receive chronic warfarin therapy to prolong PT to 1.3 to 1.5 × control (INR, 2.0 to 3.0).[28] In addition, patients with atrial fibrillation and uncontrolled hyperthyroidism have a high embolic risk and should receive anticoagulation until a euthyroid state and reversion to sinus rhythm have been achieved.

Medium risk: This category includes patients with atrial fibrillation and other forms of organic heart disease, also known as nonvalvulopathic atrial fibrillation. These patients have an intermediate but incompletely defined risk of embolism, and account for almost 50% of cardioembolic strokes. In a retrospective study,[29] patients who received anticoagulants had a much lower incidence of systemic embolism than did those patients who did not. The results of the randomized Copenhagen Atrial Fibrillation Aspirin-Anticoagulation (AFASAK) trial[30] suggest that, in patients with nonvalvulopathic atrial fibrillation, warfarin reduced the incidence of stroke and transient ischemic attacks by 75%, whereas aspirin produced no better results than placebo. Although these results support the use of warfarin, the patient subgroups that stand to gain the most benefit from anticoagulation have not yet been differentiated. When indicated, the dose of warfarin should be adjusted to prolong the PT to 1.3 to 1.5 × control (INR, 2.0 to 3.0).

Left ventricular mural thrombi develop in up to one-third of patients with acute anterior myocardial infarction; systemic embolism develops in approximately 10% of cases of mural thrombosis, thus affecting 2 to 5% of

patients with acute infarction. The incidence of embolism is highest in the first weeks after infarction, and short-term anticoagulation has been shown to reduce the embolic rate by 25 to 75%.[31–33] Two recent studies[14,34] showed that high-dose subcutaneous heparin (12,500 U administered twice daily) significantly reduced the incidence of mural thrombosis in patients with anterior infarcts. Patients with large anterior infarcts, as well as those with heart failure or atrial fibrillation, should be treated with heparin (aimed at an activated thromboplastin time of 1.5 to 2.0 × control); heparin may be followed by warfarin (PT of 1.3 to 1.5 × control; INR, 2.0 to 3.0) in patients with electrocardiographic evidence of mural thrombi or extensive wall-motion abnormalities. Warfarin may be discontinued after 1 to 3 months, except in patients with heart failure, significant ventricular dysfunction, or persistent echocardiographic evidence of mural thrombi.[35]

In addition, patients with dilated cardiomyopathy are at a medium risk for systemic embolism. In a retrospective study[36] of patients with idiopathic dilated cardiomyopathy, those treated with anticoagulants had no embolic events, whereas those who were not anticoagulated had an embolic rate of 3.5% per year. Thus, chronic warfarin therapy (PT of 1.3 to 1.5; INR, 2.0 to 3.0) is recommended to these patients.

Low risk: At the lower end of the spectrum are patients younger than age 60 with atrial fibrillation without evidence of organic heart disease (lone or idiopathic fibrillation), and those with chronic left ventricular aneurysm (more than 3 months after acute infarction). The risk of embolism is low for these patients[37,38]; therefore, chronic anticoagulation is usually unnecessary.

In summary, cardiac chamber thrombosis and embolism are related to activation of the coagulation system. Anticoagulant therapy (of variable intensity) is recommended for patients at high and medium risk, whereas those at low risk may not require this treatment (Table I).

Prosthetic valves: The thrombogenicity of heart valve prostheses involves activation primarily of the coagulation system, and, secondarily, of platelets. The risk of thromboembolism is considerably greater for mechanical than for biologic devices.

High risk: This group includes patients with mechanical prostheses and prior embolism, and those with old mechanical prostheses (implanted before the mid-1970s). Adequate warfarin therapy, at a dose sufficient to prolong the PT to 1.5 to 2.0 × control (INR, 3.0 to 4.5) is the most important factor for the prevention of thromboembolism. In the high-risk group, the addition of dipyridamole (300 to 400 mg/day) to warfarin may reduce the thromboembolic risk.[39–42] The combination of aspirin and warfarin was also effective in some trials,[43,44] but the risk of gastrointestinal bleeding was substantial when aspirin was given at a daily dose of 500 mg or more.[40] Therefore, we recommend supplementing warfarin with dipyridamole in high-risk patients with mechanical prostheses.

Medium risk: This category includes all other patients with mechanical prostheses. These patients should receive chronic anticoagulant therapy, aimed at a PT of 1.5 to 2.0 × control (INR, 3.0 to 4.5). It also includes patients with biologic prostheses (particularly in the mitral position) during the first 3 months after operation and in the presence of atrial fibrillation.[5,6] These patients should be treated with warfarin postoperatively in order to achieve a PT of 1.3 to 1.5 × control (INR, 2.0 to 3.0) for about 3 months. However, if atrial fibrillation persists anticoagulation therapy for these patients should be continued indefinitely.

Low risk: Patients with bioprostheses who maintain normal sinus rhythm postoperatively and who do not have associated left ventricular dysfunction are at low risk of thromboembolism. Patients with aortic prostheses are at particularly low risk and may be managed without antithrombotic therapy.[6]

In summary, activation of the coagulation system and secondary activation of platelets occur in patients with prosthetic heart valves. For those at high risk, combination therapy with an anticoagulant and a platelet inhibitor is recommended. Medium-risk patients can be managed with an anticoagulant alone, and antithrombotic treatment is usually not necessary for those at low risk (Table I).

CONCLUSIONS

A rational antithrombotic approach for patients with cardiovascular disease can be formulated along the lines of anatomic location of thromboembolism, pathogenesis and risk identification.[45] Patients at high risk require aggressive antithrombotic therapy with either the combination of a platelet inhibitor and an anticoagulant (in arterial disease and valvular prostheses), or relatively high intensity anticoagulation (in cardiac chamber thrombosis). Patients at medium risk can be managed with a platelet inhibitor alone (in arterial disease) or an anticoagulant (in cardiac chamber thrombosis or prosthetic valves). Finally, patients at the lowest spectrum of risk usually do not require antithrombotic therapy.

REFERENCES

1. Fuster V, Badimon L, Cohen M, Ambrose JA, Badimon JJ, Chesebro JH. Insights into the pathogenesis of acute ischemic syndromes. *Circulation 1988; 77:1213–1220.*

2. Badimon L, Badimon JJ, Galvez A, Chesebro JH, Fuster V. Influence of arterial wall damage and wall shear rate on platelet deposition: ex vivo study in a swine model. *Arteriosclerosis 1986;6:312–320.*

3. Fuster V, Halperin JL. Left ventricular thrombi and cerebral embolism. *N Engl J Med 1989;320:392–394.*

4. Cabin HS, Roberts WC. Left ventricular aneurysm, intraaneurysmal thrombus and systemic embolus in coronary heart disease. *Chest 1980;77:586–590.*

5. Chesebro JH, Adams PC, Fuster V. Antithrombotic therapy in patients with valvular heart disease and prosthetic heart valves. *JACC 1986;8:suppl B:41B–56B.*

6. Edmunds LH. Thrombotic and bleeding complications of prosthetic heart valves. *Ann Thorac Surg 1987;44:430–445.*

7. Lewis HD, Davis JW, Archibald DG, Steinke WE, Smitherman TC, Doherty JE, Schapner HW, LeWinter MM, Linares E, Pouget JM, Sabharwal SC, Chesler E, DeMots H. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative Study. *N Engl J Med 1983;309:396–403.*

8. Cairns JA, Gent M, Singer J, Finnie KJ, Forggatt GM, Holder DA, Jablonsky G, Kostuk WJ, Melendez LJ, Myers MG, Sackett DL, Sealy BJ, Tanser PH. Aspirin, sulfinpyrazone, or both in unstable angina. *N Engl J Med 1985;313: 1369–1375.*

9. Theroux P, Ouimet H, McCans J, Latour JG, Joly P, Levy G, Pelletier E, Juneau M, Stasiak J, deGuise P, Pelletier GB, Rinzler D, Waters DD. Aspirin, heparin, or both to treat unstable angina. *N Engl J Med 1988;319:1105–1111.*

10. Violi F, Scrutinio D, Cimminiello C, Gamba G, Rudelli G, Chierichetti SM, Rizzoni P, Balsano F. S.T.A.I. (study of ticlopidine in unstable angina) (abstr). *JACC 1989;13:suppl A:238A.*
11. Telford AM, Wilson C. Trial of heparin versus atenolol in prevention of myocardial infarction in intermediate coronary syndrome. *Lancet 1981;1:1225–1228.*
12. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group: Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet 1988;2:349–360.*
13. Chalmers TC, Matta RJ, Smith H, Kunzler AM. Evidence favoring the use of anticoagulants in the hospital phase of acute myocardial infarction. *N Engl J Med 1977;297:1091–1096.*
14. The SCATI (Studio sulla Caleiparina nell' Angina e nella Trombose Ventriculare nell' Infarcto) Group. Randomised controlled trial of subcutaneous calcium-heparin in acute myocardial infarction. *Lancet 1989;2:182–186.*
15. Barnathan ES, Schwartz JS, Taylor L, Laskey WK, Kleaveland JP, Kussmaul WG, Hirshfeld JW. Aspirin and dipyridamole in the prevention of acute coronary thrombosis complicating coronary angioplasty. *Circulation 1987;76:125–134.*
16. Schwartz L, Bourassa MG, Lesperance J, Aleridge HE, Kazim F, Salvatori VA, Henderson M, Bonan R, David PR. Aspirin and dipyridamole in the prevention of restenosis after percutaneous transluminal coronary angioplasty. *N Engl J Med 1988;318:1714–1719.*
17. White CW, Chaitman B, Lassar TA, Marcus ML, Chisholm RJ, Knudson M, Morton B, Roy L, Khaja F, Vandormeal M, Reitman M. Antiplatelet agents are effective in reducing the immediate complications of PTCA: results from the ticlopidine multicenter trial (abstr). *Circulation 1987;76:suppl IV:IV-400.*
18. Heras M, Chesebro JH, Penny WJ, Bailey L, Lam LYT, Holmes DR, Reeder GS, Badimon L, Fuster V. Importance of adequate heparin dosage in arterial angioplasty in a porcine model. *Circulation 1988;78:654–660.*
19. Chesebro JH, Clements IP, Fuster V, Elveback LR, Smith HC, Bardsley WT, Frye RL, Holmes DR, Vlietstra RE, Pluth JR, Wallace RB, Puga FJ, Orszulak TA, Piehler JM, Schaff HV, Danielson GK. A platelet inhibitor-drug trial in coronary-artery bypass operations. Benefit of perioperative dipyridamole and aspirin therapy on early postoperative vein-graft patency. *N Engl J Med 1982;307:73–78.*
20. Limet R, David JL, Maggotteau P, Larock MP, Rigo P. Prevention of aorta-coronary bypass graft occlusion. *J Thorac Cardiovasc Surg 1987;94:773–783.*
21. Goldman S, Copeland J, Moritz T, Henderson W, Zadina K, Ovitt T, Doherty J, Read R, Chesler E, Sako Y, Lancaster L, Emery R, Sharma GVRK, Josa M, Pacold I, Montoya A, Parikh D, Sethi G, Holt J, Kirklin J, Shabetai R, Moores W, Alridge J, Masud Z, DeMots H, Floten S, Haakenson C, Harker LA. Improvement in early saphenous vein graft patency after coronary artery bypass surgery with antiplatelet therapy: results of a Veterans Administration Cooperative Study. *Circulation 1988;77:1324–1332.*
22. Chesebro JH, Webster MWI, Smith HC, Frye RL, Holmes DR, Reeder GS, Bresnahan DR, Nishimura RA, Clements IP, Bardsley WT, Grill DE, Fuster V. Antiplatelet therapy in coronary disease progression: Reduced infarction and new lesion formation (abstr). *Circulation 1989;80:suppl II:II–266.*
23. Antiplatelet Trialists' Collaboration. Secondary prevention of vascular disease by prolonged antiplatelet treatment. *Br Med J 1988;296:320–331.*
24. Report of the Sixty Plus Reinfarction Study Research Group. A double-blind trial to assess long-term oral anticoagulant therapy in elderly patients after myocardial infarction. *Lancet 1980;2:989–993.*
25. Smith P, Arnesen H. Oral anticoagulants reduce mortality, reinfarction and cerebrovascular events after myocardial infarction—WARIS Study (abstr). *Eur Heart J 1989;10:suppl:264.*
26. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med 1989;321:129–135.*
27. Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Janrozik K, Warlow C, Hafner B, Thompson E, Norton S, Gilliland J, Doll R. A randomized trial of the effects of prophylactic daily aspirin among male British doctors. *Br Med J 1988;296:313–316.*
28. Dunn M, Alexander J, deSilva R, Hildner F. Antithrombotic therapy in atrial fibrillation. *Chest 1989;95:suppl:118S–127S.*
29. Roy D, Marchand E, Gagne P, Chabot M, Cartier R. Usefulness of anticoagulant therapy in the prevention of embolic complications of atrial fibrillation. *Am Heart J 1986;112:1039–1043.*
30. Petersen P, Godtfredsen J, Boysen G, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK Study. *Lancet 1989;1:175–179.*
31. Report of the Working Party on Antiocoagulation Therapy in Coronary Thrombosis to the Medical Research Council. Assessment of short-term anticoagulation administration after cardiac infarction. *Br Med J 1969;1:335–342.*
32. Drapkin A, Merskey C. Anticoagulation therapy after acute myocardial infarction. Relation of therapeutic benefit to patient's age, sex and severity of infarction. *JAMA 1972;222:541–548.*
33. Veterans Administration Hospital Investigators. Anticoagulants in acute myocardial infarction. Results of a cooperative clinical trial. *JAMA 1973;225:724–729.*
34. Turpie AGG, Robinson JG, Doyle DJ, Mulji AS, Mishkel GJ, Sealy BJ, Cairns JA, Skingley L, Hirsh J, Gent M. Comparison of high-dose with low-dose subcutaneous heparin to prevent left ventricular mural thrombosis in patients with acute transmural anterior myocardial infarction. *N Engl J Med 1989;320:352–357.*
35. Stratton JR, Resnick AD. Increased embolic risk in patients with left ventricular thrombi. *Circulation 1987;75:1004–1011.*
36. Fuster V, Gersh BJ, Giuliani ER, Tajik AJ, Brandenburg RO, Frye RL. The natural history of idiopathic dilated cardiomyopathy. *Am J Cardiol 1981;47:525–531.*
37. Kopecky SL, Gersh BJ, McGoon MD, Whisnant JP, Holmes DR, Ilstgrup DM, Frye RL. The natural history of lone atrial fibrillation: A population-based study over three decades. *N Engl J Med 1987;317:669–674.*
38. Lapeyre AC, Steele PP, Kazmier FJ, Chesebro JH, Vlietstra RE, Fuster V. Systemic embolism in chronic left ventricular aneurysm: incidence and the role of anticoagulation. *JACC 1985;6:534–538.*
39. Sullivan JM, Harken DE, Gorlin R. Pharmacologic control of thromboembolic complications of cardiac-valve replacement. *N Engl J Med 1971;284:1391–1394.*
40. Chesebro JH, Fuster V, Elveback LR, McGoon DC, Pluth JR, Puga FJ, Wallace RB, Danielson GK, Orszulak TA, Piehler JM, Schaff HV. Trial of combined warfarin plus dipyridamole or aspirin therapy in prosthetic heart valve replacement. Danger of aspirin compared with dipyridamole. *Am J Cardiol 1983;51:1537–1541.*
41. Kasahara T. Clinical effect of dipyridamole ingestion after prosthetic heart valve replacement—especially on the blood coagulation system. *J Jpn Assoc Thorac Surg 1977;25:1007–1021.*
42. Rajah SM, Sreeharan N, Joseph A, Watson DA. A prospective trial of dipyridamole and warfarin in heart valve patients (abstr). *Acta Therapeutica 1980;6:suppl 93:54.*
43. Dale J, Myhre E, Storstein O, Stomorken H, Eksking L. Prevention of arterial thromboembolism with acetylasalicyclic acid: a controlled clinical study in patients with aortic ball valves. *Am Heart J 1977;94:101–111.*
44. Altman R, Boullon F, Rouvier J, Raca R, de la Fuente L, Favaloro R. Aspirin and prophylaxis of thromboembolic complications in patients with substitute heart valves. *J Thorac Cardiovasc Surg 1976;72:127–129.*
45. Stein B, Fuster V, Halperin JL, Chesebro JH. Antithrombotic therapy in cardiac disease: an emerging approach based on pathogenesis and risk. *Circulation 1989;80:1501–1513.*

Diagnosis of Venous Thrombosis and Pulmonary Embolism

Jack Hirsh, MD

Venous thrombosis and pulmonary embolism are closely related disorders. As many as 70 to 80% of patients with pulmonary embolism have associated proximal deep venous thrombosis. The clinical diagnosis alone of both venous thrombosis and pulmonary embolism is inaccurate because of the insensitivity and nonspecificity of findings, a problem that also occurs with a variety of other disorders. Invasive, objective tests are still the reference standard, but they are not always easy to perform, they cannot be used for a considerable number of very ill patients, and they create some patient discomfort. There is an increasing trend toward using noninvasive methods, either alone or in combination. These methods entail less risk, can be performed more quickly and conveniently, and are usually more cost-effective. Practical approaches to diagnosing venous thrombosis and pulmonary embolism in the clinical setting are discussed.

(Am J Cardiol 1990;65:45C–49C)

From the Hamilton Civic Hospitals Research Centre, and McMaster University, Hamilton, Ontario, Canada.

Address for reprints: Jack Hirsh, MD, Hamilton Civic Hospitals Research Centre, Henderson General Division, 11 Concession Street, Hamilton, Ontario L8V 1C3, Canada.

The common clinical manifestations of deep venous thrombosis are local pain, tenderness and swelling. The differential diagnosis includes the following conditions that may be confused with venous thrombosis: ruptured Baker's cyst, cellulitis, muscle tear, muscle cramp, hematoma, external compression of the iliac vein, heart failure, varicose veins, leg immobilization, lymphedema, lipedema, self-induced edema and the postphlebitic syndrome.

Before 1970, most physicians and hospitals in North America used clinical diagnosis exclusively to make management decisions in patients with suspected venous thrombosis. Data published about 1970 and subsequently have firmly established that the clinical diagnosis of venous thrombosis is inaccurate because clinical findings are both insensitive and nonspecific. Sensitivity is low because many potentially dangerous venous thrombi are nonocclusive and therefore clinically silent. Specificity is low because symptoms and signs of venous thrombosis can all be caused by nonthrombotic disorders.

Patients with mild symptoms may have serious venous thrombosis; it is essential that these patients be treated. On the other hand, it is important not to treat patients unnecessarily or to overdiagnose venous thrombosis. In our experience, compatible with that of many others, 70% of patients investigated for clinically suspected venous thrombosis did not have the diagnosis confirmed by objective tests. These patients included many who were told, incorrectly, that they had so-called recurrent intractable thrombosis—a chronic, potentially fatal disease—engendering significant and totally unnecessary anxiety.

The careful documentation of symptoms and signs in patients with clinically suspected deep-vein thrombosis, although not helpful in establishing a diagnosis of venous thrombosis in most patients, may nevertheless be valuable for identifying or excluding other disorders that readily lend themselves to clinical diagnosis. But whenever another diagnosis cannot clearly be established by clinical examination, objective tests are necessary to confirm or exclude the diagnosis of venous thrombosis.

INVASIVE DIAGNOSIS OF VENOUS THROMBOSIS

Venography is accepted as the reference standard for diagnosing venous thrombosis. The aim of venography is to outline the deep venous system of the legs by injecting a radiopaque contrast medium into a dorsal foot vein. When good technique is used, ascending venography outlines the entire deep venous system of the lower legs, including the external and common iliac veins in most patients. However, common femoral and iliac venogra-

TABLE I Venography

Pros
Diagnostic standard for venous thrombosis
Outlines entire deep venous system of lower extremities, including external and common iliac veins
Cons
Invasive
Requires expertise to administer and interpret
Inferior vena cava, internal iliac, and deep femoral vein not visualized

TABLE II Fibrinogen Leg Scanning

Pros
Screens high-risk patients
Noninvasive
Complements IPG in diagnosis exclusion or confirmation
Detects 90% of acute calf vein thrombi
Cons
Requires hours or days before definitive result available
Insensitive to proximal venous thrombi
Increases the expense

IPG = impedance plethysmography.

phy may be needed if the external and common iliac veins are not properly visualized by the ascending technique or if the inferior vena cava must be outlined. The most reliable criterion for diagnosing thrombosis is the presence of an intraluminal filling defect that is constant in all x-ray films and is seen in a number of projections.

Venography is difficult to perform and requires considerable experience to execute and to interpret. Radiologists and clinicians must be sensitive to the pitfalls of this technique, and must either repeat venography when tests are inadequate or base their diagnoses on noninvasive tests.

Table I summarizes the advantages and disadvantages of venography in the diagnosis of venous thrombosis.

NONINVASIVE DIAGNOSIS OF VENOUS THROMBOSIS

Noninvasive methods for the diagnosis of venous thrombosis include: ^{125}I-fibrinogen scanning, impedance plethysmography (IPG), Doppler ultrasonography and B-mode ultrasonography.

Fibrinogen scanning: ^{125}I-fibrinogen leg scanning depends on incorporation of circulating radioiodine-labeled fibrinogen into the thrombus. The resulting radioactive fibrin is then detected by measuring the increase of overlying surface radioactivity with an isotope detector. Although very limited as a diagnostic test in patients with clinically suspected thrombosis, fibrinogen scanning can be used to screen medically and surgically treated patients who are at high risk of developing venous thrombosis. It can also be used to complement IPG in confirming or excluding the diagnosis of clinically suspected thrombosis. It has been demonstrated that if both the ^{125}I-fibrinogen scan and the impedance plethysmogram yield negative results, the negative predictive value of that combination is as good as that of a negative result in a venogram.

Fibrinogen leg scanning detects more than 90% of acute calf vein thrombi, but detects only between 60 and 80% of proximal vein thrombi, depending on their location. Fibrinogen scanning is relatively insensitive in the upper thigh, and insensitive to venous thrombi in the pelvis. Fibrinogen scanning should never be used as the only diagnostic test because it fails to detect many high proximal vein thrombi, and also because it may take hours or even days for enough fibrinogen to accumulate in the thrombus to make the test result positive.

Table II summarizes the advantages and disadvantages of fibrinogen scanning in the diagnosis of venous thrombosis.

Impedance plethysmography: IPG is a noninvasive method that detects volume changes in the leg when a pneumatic thigh cuff is inflated and deflated, resulting in changes in electrical resistance (impedance). These changes are reduced in patients with obstruction (e.g., thrombosis) of the popliteal or proximal veins. The accuracy of IPG is critically dependent on the degree of venous filling during cuff occlusion. Venous filling is improved by prolonging the period of cuff occlusion and by using repeated sequential testing.

The IPG test is sensitive and specific for thrombosis of the popliteal, femoral or iliac vein (proximal veins). Because it detects only thrombi that produce obstruction to venous outflow, it will not detect calf vein thrombi. It may also overlook small, nonocclusive proximal vein thrombi, and may likewise be negative when proximal vein thrombosis is associated with well-developed collaterals. Finally, the IPG test does not distinguish between thrombotic and nonthrombotic obstruction to venous flow. It may therefore lead to false-positive results if the patient is positioned incorrectly or is inadequately relaxed, with constriction of veins by contraction of leg muscles; if compression is caused by an extravascular mass; or if venous outflow is raised by central venous pressure.

It is of practical clinical importance to know the frequency with which an abnormal IPG result returns to normal, because patients with proximal vein thrombosis frequently have symptoms in the affected leg during or after long-term anticoagulant therapy. The IPG returns to normal by 3 weeks for approximately 30% of patients, by 6 weeks for 50% of patients, at 3 months for 60% of patients, at 6 months for 80% and at 12 months for 90%. Because of these findings, we perform baseline IPG for all patients with proximal vein thrombosis when anticoagulant therapy is discontinued.

Table III summarizes the advantages and disadvantages of IPG in the diagnosis of venous thrombosis.

Doppler ultrasonography: Doppler ultrasonograhy was introduced and developed at about the same time as IPG, and has similar advantages and limitations. In expert hands, Doppler ultrasonography is a sensitive method for detecting proximal vein thrombosis, but it is less sensitive for detecting calf vein thrombosis. This method involves directing a beam of ultrasound energy percutaneously at an underlying vein, where it is reflected from blood cells. If the blood is stationary, no flow sound is

heard. If the blood particles are moving, the beam is reflected at a changed frequency (the Doppler shift) that is proportional to the velocity of flow and produces an audible signal, or flow sound.

This technique can be performed more conveniently and rapidly than IPG and is less expensive. It is almost as sensitive as IPG to symptomatic proximal vein thrombosis, and more sensitive to symptomatic calf vein thrombosis than IPG, detecting about 50% of such thrombosis. It can be used for patients who have their legs in plaster casts or who are in traction. Interpretation of results is subjective, however, and requires considerable skill and experience.

Table IV summarizes the advantages and disadvantages of Doppler ultrasonography in the diagnosis of venous thrombosis.

B-mode ultrasonography: B-mode ultrasonography, or duplex scanning, is a recently introduced, very promising diagnostic procedure that is being used with increasing frequency in the diagnosis of venous thrombosis. B-mode ultrasonography is performed using a high-resolution, real-time ultrasound scanner equipped with a 5-MHz electronically focused linear-array transducer. The common femoral vein is localized in the groin with the patient in the supine position. Visualization of both the femoral artery and vein is necessary. If only the artery is seen, the patient performs a Valsalva maneuver in order to obtain visualization of the vein. The presence or absence of an intraluminal echogenic band and the percentage change in vein diameter during the Valsalva maneuver can also be assessed. The femoral vein is visualized in cross section and longitudinally. The popliteal vein is localized in the popliteal fossa with the patient in the prone position.

The compressibility of the vein being examined is assessed by compressing the vein with the transducer probe and observing the effect on the monitor. The result is scored either as noncompressible, or if no residual lumen is observed, as fully compressible. Single-hand firm compression with the transducer probe is sufficient to evaluate noncompressibility. Hard copies can be obtained from the freeze-frame image of both stages of the procedure.

Like IPG and Doppler ultrasonography, B-mode ultrasonography is highly sensitive and specific for proximal vein thrombosis, but of limited sensitivity in the detection of calf vein thrombosis.

Other noninvasive tests: Less common techniques used to diagnose venous thrombosis (which have not been as thoroughly evaluated) include strain-gauge plethysmography and thermography. Blood tests that reflect intravascular fibrin formation and fibrin proteolysis are currently being evaluated.

SERIAL IMPEDANCE PLETHYSMOGRAPHY

A practical noninvasive approach to diagnosing clinically suspected venous thrombosis is based on serial IPG. It is likely that B-mode ultrasonograhy can be used in the same way. The use of serial IPG alone has been evaluated in a number of prospective studies and has been found to be effective. To date, the effectiveness and safety of

TABLE III Impedance Plethysmography

Pros
Sensitive and specific for thombosis of popliteal, femoral or iliac proximal veins
Useful for monitoring patients after anticoagulant therapy is discontinued
Noninvasive
Cons
Does not detect calf vein or small proximal vein thrombi
Does not distinguish between thrombotic and nonthrombotic obstruction
False-positive results from incorrect patient position, contracted leg muscles, the presence of extravascular mass, or elevated central venous pressure

TABLE IV Doppler Ultrasonography

Pros
Sensitive for proximal vein thrombosis
Noninvasive, rapid, inexpensive
Easily performed
50% sensitive to symptomatic calf vein thrombosis
Cons
Interpretation subjective and requires expertise

Doppler ultrasonography alone, and of B-mode ultrasonograhy, have not been formally evaluated.

Repeated studies have demonstrated that untreated symptomatic calf vein thrombi only very rarely cause serious thromboembolic events if the thrombus does not extend from the calf. But the thrombus does extend in about 20 to 30% of patients with symptomatic calf vein thrombosis, usually within about 7 days of the thrombus onset.

Repeated IPG is based on this confirmed observation that calf vein thrombi are clinically important only when they extend into the proximal veins, at which point detection with IPG becomes possible. By performing repeated IPG examinations of patients with clinically suspected venous thrombosis, it is possible to identify patients with extending calf vein thrombosis who can be appropriately treated.

An algorithm (Fig. 1) for the noninvasive diagnosis of clinically suspected venous thrombosis is as follows: IPG (or B-mode ultrasonograhy) is performed when the patient is referred; if the IPG result is positive, and in the absence of clinical conditions that are known to produce false-positive results, the diagnosis of venous thrombosis is established, and the patient is treated accordingly. If the result of the initial test is negative, anticoagulant therapy is withheld and the test is repeated the following day, again on day 5, and on days 10 to 14. If the impedance plethysmogram or B-mode ultrasonogram yields positive results during this time, a diagnosis of venous thrombosis is made, and anticoagulant therapy is begun. A positive impedance plethysmogram result in the presence of conditions known to produce a false-positive result (e.g. congestive heart failure) should be confirmed by venography.

If noninvasive tests are not available, a clinical suspicion of venous thrombosis should be objectively confirmed or excluded by performing ascending venography.

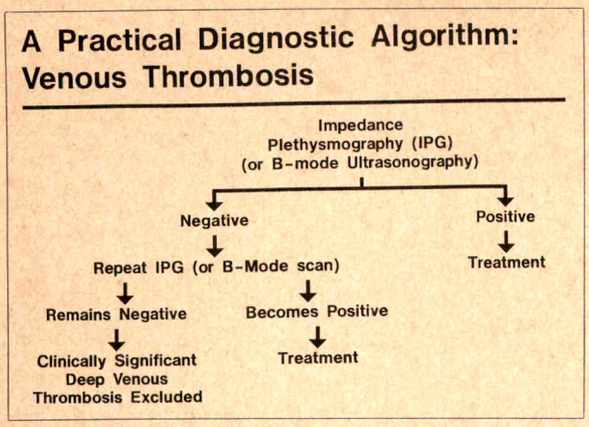


FIGURE 1. An algorithm for the noninvasive diagnosis of clinically suspected venous thrombosis, using serial impedance plethysmography or B-mode ultrasonograhy.

PULMONARY EMBOLISM

Pulmonary embolism is a common complication of deep venous thrombosis of the legs. As many as 70 to 80% of patients with pulmonary embolism have leg vein thrombosis by venography at the time of clinical presentation.

The clinical diagnosis of pulmonary embolism is as nonspecific as the clinical diagnosis of venous thrombosis, because all the symptoms and signs of pulmonary embolism can be caused by other cardiorespiratory disorders. More than half of all patients with clinically suspected pulmonary embolism do not have this diagnosis confirmed by objective testing.

Arterial blood gas measurements are almost as nonspecific as clinical diagnosis and should not be used to make a diagnosis of pulmonary embolism. In addition, normal PaO_2 (>80 mm Hg) does not exclude the possibility of an embolism.

The radiologic findings associated with pulmonary embolism are also nonspecific and may show no abnormality. However, the chest x-ray may reveal other causes of the patient's condition (e.g., pneumothorax), and it is also required for interpretation of the lung-scan findings.

An electrocardiogram may be useful in differentiating between pulmonary embolism and myocardial infarction, but the electrocardiogram is frequently normal or nonspecific. The time-honored findings of right-axis shift and the S_1, Q_3, T_3 pattern are uncommon and also nonspecific.

Lung scanning is extremely useful—when the result is normal—to exclude a diagnosis of pulmonary embolism. When there is a large ventilation-perfusion mismatch, lung scanning can be used to diagnose pulmonary embolism. Other lung-scan findings do not have sufficiently high or low predictive power either to rule out or to rule in pulmonary embolism, and a diagnosis of pulmonary embolism requires pulmonary angiography to confirm it. Objective tests for venous thrombosis are also useful because, as mentioned earlier, most pulmonary emboli are associated with deep-vein thrombosis of the legs.

Most pulmonary emboli are clinically silent. When manifested, their signs and symptoms include transient dyspnea and tachypnea, and the syndrome of pulmonary infarction or congestive atelectasis (also known as ischemic pneumonitis or incomplete infarction), which is associated with pleuritic chest pain, cough, hemoptysis, pleural effusion and pulmonary infiltrates on chest x-ray.

Other clinical manifestations of pulmonary emboli can include right-sided cardiac failure associated with severe dyspnea and tachypnea; cardiovascular collapse with hypotension, syncope and coma; and various less common and less specific clinical features, including confusion and coma, pyrexia, wheezing, resistant heart failure and unexplained arrhythmia.

The differential diagnosis of shortness of breath includes atelectasis, pneumothorax, pneumonia, acute bronchitis, acute bronchiolitis, and acute bronchial obstruction due to mucus plugging, bronchoconstriction or acute pulmonary edema.

Pleuritic-type chest pain may be a prominent feature of musculoskeletal abnormalities of the chest wall, in-

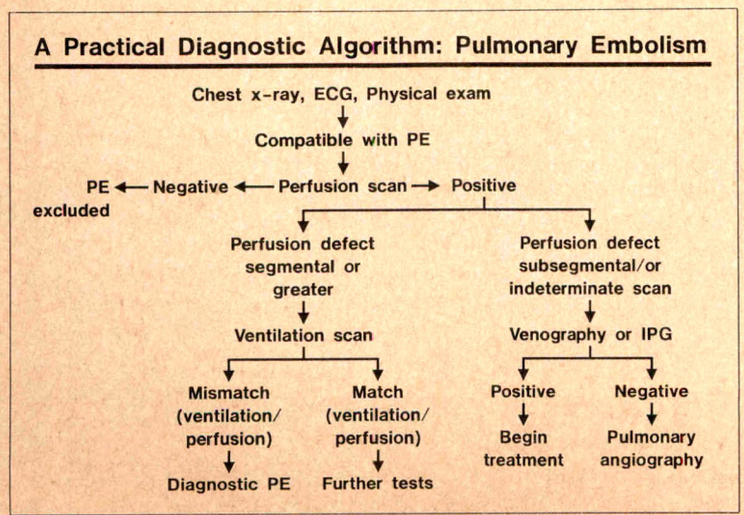


FIGURE 2. A diagnostic algorithm for the management of clinically suspected pulmonary embolism. ECG = electrocardiogram; IPG = impedance plethysmography; PE = pulmonary embolism.

cluding fractured ribs, myositis, muscle strain, and occasionally acute pericarditis.

Hemoptysis associated with pulmonary embolism must be differentiated from hemoptysis caused by bronchitis, bronchogenic carcinoma, tuberculosis, mitral stenosis, bronchial adenoma and bronchiectasis.

If acute right ventricular heart failure complicates pulmonary embolism, it is almost always associated with severe dyspnea and tachypnea. These features can also be due to acute pulmonary hypertension, which complicates left ventricular failure, acute infection in patients with severe chronic obstructive lung disease, and pulmonary emboli of nonthrombotic origin.

Acute pulmonary hypertension can complicate mitral stenosis or acute left ventricular failure, which is most frequently caused by acute myocardial infarction. In patients with chronic obstructive lung disease, acute pulmonary hypertension, severe dyspnea and right-sided cardiac failure may develop when the course of their illness is complicated by acute chest infection.

Finally, myocardial infarction complicated by cardiogenic shock, acute pericardial tamponade, acute massive blood loss and gram-negative septicemia may be confused with massive embolism.

PULMONARY ANGIOGRAPHY

Pulmonary angiography is the reference standard for establishing the presence or absence of pulmonary embolism. The diagnostic resolution of pulmonary angiography is improved, and the risk of the procedure is reduced by using selective angiography and magnification views. A well performed pulmonary angiogram that has negative results excludes a diagnosis of pulmonary embolism.

Selective pulmonary angiography is a safe technique as long as patients do not have severe chronic hypertension or severe cardiac or respiratory decompensation. Approximately 20% of patients with clinically suspected pulmonary embolism and abnormal perfusion lung-scan findings cannot undergo pulmonary angiography because of the severity of their primary illness. Because of the limitations of pulmonary angiography, extensive efforts have been made to replace this invasive technique with less invasive diagnostic tests.

NONINVASIVE DIAGNOSIS OF PULMONARY EMBOLISM

Perfusion lung scans and ventilation lung scans are used in the noninvasive diagnosis of pulmonary embolism. To accomplish perfusion lung scanning, particles of human macroaggregated albumin labeled with ^{131}I are trapped in the pulmonary capillary bed, and their distribution, reflecting the distribution of lung blood flow, is recorded with an external photoscanner. Improvements in instrumentation, particularly the development of the gamma camera, as well as more effective radiopharmaceuticals, have led to wide acceptance of this technique for investigating pulmonary embolism.

Although perfusion lung scanning can detect regions of poor perfusion as small as 2 cm in diameter, an abnormal perfusion scan is nonspecific and cannot identify the cause of the perfusion defect. A number of studies have confirmed the poor specificity of perfusion lung scanning for diagnosing pulmonary embolism. In a recent prospective study of a consecutive series of 305 patients with suspected embolism and abnormal perfusion lung-scan findings, pulmonary embolism was demonstrated by angiography in only 95 of 183 patients (52%).[1]

Ventilation lung scanning uses either radioactive gases or radioactive aerosols that are inhaled and exhaled by the patient while a gamma camera records the distribution of radioactivity within the alveolar gas exchange units. Ventilation imaging was introduced on the assumption that ventilation is preserved in areas that have reduced perfusion because of pulmonary embolism (ventilation-perfusion mismatch), whereas ventilation is abnormal when perfusion defects occur as a consequence of primary ventilation abnormalities (ventilation-perfusion match). This assumption has recently been shown to be only partly correct.

A DIAGNOSTIC ALGORITHM

A diagnostic algorithm for the management of clinically suspected pulmonary embolism may be offered (Fig. 2). After the history and physical examination, electrocardiogram, and chest x-ray, all patients should undergo perfusion lung scanning. Finding negative results on a perfusion lung scan rules out clinically significant pulmonary embolism, and anticoagulant therapy is withheld. If the perfusion lung scan shows 1 or more segmental (or greater) perfusion defects, ventilation lung scanning should be performed because the probability of pulmonary embolism is markedly increased if a mismatch is found (positive predictive value, 86%). This provides an end point for begining anticoagulant therapy for most patients. A matched ventilation-perfusion defect does not rule out the possibility of pulmonary embolism, and further objective testing is required for these patients.

Similarly, when patients have small perfusion defects (1 or more subsegmental defects), or when patients have indeterminate lung-scan findings (in which the perfusion-scan defects correspond to a defect shown on the chest x-ray), the predictive values obtained from these ventilation-perfusion-scan patterns are neither sufficiently high or low to confirm or exclude pulmonary embolism. For these patients, venography or IPG could be performed as the initial step of the diagnostic workup.

If objective testing confirms the presence of deep-vein thrombosis, anticoagulant therapy can begin without the need to perform pulmonary angiography. If results of venography are negative, however, pulmonary angiography is required to confirm the presence or absence of pulmonary embolism.

REFERENCES

1. Hull RD, Hirsh J, Carter CJ, et al. Diagnostic value of ventilation-perfusion lung scanning in patients with suspected pulmonary embolism. *Chest 1985;88: 819–828.*

Prevention of Venous Thrombosis and Pulmonary Embolism

Vijay Kakkar, MD, FRCSE

Deep vein thrombosis (DVT) leads to hospitalization for up to 600,000 persons each year in the United States. Venous thrombosis in itself may be benign, but the condition can lead to dangerous complications and has a high recurrence rate. Strategies to prevent DVT involve prevention of stasis and reversal of changes in blood coagulability that allow thrombi to form.

Pharmacologic agents have been effective in reducing the incidence of DVT and pulmonary embolism. Low-dose subcutaneous heparin is considered a nearly ideal DVT preventative for surgically treated patients. The risk of hemorrhage is the main limitation to routine use of subcutaneous anticoagulants for DVT, but careful patient selection can minimize that risk. After anticoagulant therapy with heparin, generally for 7 to 10 days, oral warfarin is the drug of choice for maintenance anticoagulation to prevent DVT recurrence. Therapy for pulmonary embolism is the same as for DVT—immediate anticoagulation with heparin followed by maintenance with warfarin.

(Am J Cardiol 1990;65:50C–54C)

From the Thrombosis Research Unit, King's College School of Medicine and Dentistry, London, England.

Address for reprints: Professor Vijay Kakkar, MD, King's College School of Medicine and Dentistry, Denmark Hill, London SE5 8RX, England.

Deep vein thrombosis (DVT) is a frequent complication of certain primary illnesses and medical procedures, and up to 600,000 persons with this condition are hospitalized each year in the United States. Although relatively benign in itself, venous thrombosis carries with it the risk of such late sequelae as swelling of the legs, varicose veins, ulceration and other circulatory changes. Furthermore, it has a high recurrence rate.

A high percentage of calf-vein thrombi undergo spontaneous lysis, but in about 20% of patients more extensive thrombi develop that may extend proximally into larger veins. Nearly 50% of pulmonary emboli arise from these extended venous thrombi. The problem of treatment of these emboli is that two-thirds of the deaths that follow pulmonary embolism (PE) occur within 30 minutes of the embolic event.[1] Therefore, thrombolytic treatment is not beneficial, even though it is capable of producing rapid lysis of emboli. In fact, 80% of PEs occur without symptoms of peripheral DVT, and therefore treatment with anticoagulants and heparin is not initiated. Thus, prevention is the optimal form of management in patients after surgery and other patients at high risk of DVT or PE developing.

DEEP VEIN THROMBOSIS PROPHYLAXIS VIA PREVENTION OF STASIS

Although the mechanism is unclear, both stasis in the deep veins of the leg and changes in coagulability of the blood contribute to the formation of venous thrombi in the calves. Thus, strategies for preventing DVT aim to prevent stasis and to reverse coagulability changes that allow thrombi to form.

Several approaches used to prevent venous stasis in surgically treated patients have yielded mixed results. Some of these methods are cost-effective and beneficial, at least for low-risk patients. Such methods include wearing elastic stockings to increase venous return, performing vigorous leg exercises before and after surgery, elevating the foot of the bed and early postoperative ambulation.

Another approach to preventing stasis intraoperatively is electrical stimulation of the calf muscles with a low voltage current.[2] Another method involves rhythmic compression of the calves.[3]

Although these methods, particularly the last 2, are effective for lessening stasis and reducing the incidence of venous thrombosis in all but high-risk patients, they are somewhat inconvenient to use and have a number of logistical and management drawbacks.

DEEP VEIN THROMBOSIS PROPHYLAXIS WITH ANTITHROMBOTIC THERAPY

The use of various pharmacologic agents to counteract blood coagulability has been more productive. These agents can be broadly classified into 3 main groups: (1) drugs that alter platelet function, (2) drugs that interfere with the coagulation mechanism, and (3) drugs that increase endogenous fibrinolytic activity.

Alteration of platelet function: One theory of thrombus formation is that it is initiated at a site of presumed damage to the venous epithelium, with subsequent platelet aggregation. The rationale for using drugs that alter platelet function is that by preventing platelet aggregation they can prevent thrombus formation. The agents most often used are aspirin, dextran and dipyridamole.

Aspirin irreversibly inactivates the cyclooxygenase of exposed platelets. This effect lasts for the life span of these exposed platelets. Results of studies with rabbits have been conflicting,[4,5] and 2 double-blind studies[6,7] have shown that aspirin does not reduce the incidence of venous thrombosis after elective general surgery. A later study[8] found an impressive and statistically significant decrease in venous thrombosis in men, but not in women, after elective hip replacement. Another study showed that aspirin prevented PE after hip fracture.[9]

An interesting finding in several of the studies was that, whereas the incidence of DVT was lower in aspirin-treated patients, the incidence of PE was unchanged in controls. An explanation of this effect may be that aspirin confounded the diagnosis of some DVT cases by masking pain, tenderness, and increased temperature. Another possible explanation is that aspirin prevents the synthesis and release from platelets of prostaglandins, known to be mediators of the inflammatory response.

Dextran 70 is frequently used to prevent venous thrombosis. The rationale for its use as prophylaxis is that its infusion is followed by a decrease in platelet adhesiveness and by a defect in the release reaction of platelets and of platelet aggregation. Its exact mechanism of action is unclear, but it may increase the electrical negativity of platelets and also lower the plasma level of the von Willebrand factor. Fibers in clots formed in the presence of dextran are coarser, with decreased tensile strength and increased susceptibility to lysis by plasmin. Dextrans are also volume expanders, which may increase blood flow and prevent venous stasis. Two large studies[10,11] demonstrated dextran's effectiveness in reducing the incidence of fatal postoperative PE.

Complications with use of dextran include PE in patients with limited cardiac reserve, occasional renal failure, mild allergic reactions and, rarely, anaphylactic reactions. Other disadvantages include the drug's cost and the necessity for intravenous administration. Nonetheless, dextran is effective in selected patients.

Dipyridamole, a weak inhibitor of adenosine diphosphate-induced platelet aggregation, is effective in preventing experimentally induced thrombosis.[12] Combinations of dipyridamole plus aspirin and other compounds have been tried, but studies of their value as prophylactics are inconclusive.[13]

Interference with the coagulation mechanism: Another pharmacologic approach uses drugs such as oral anticoagulants (e.g., warfarin sodium) or low-dose subcutaneous heparin, which block or alter coagulation. There has also been a recent trial of a third group of compounds that act by releasing endogenous heparin-like substances.

Warfarin and other oral anticoagulants: Warfarin and other oral anticoagulants are the most effective method of preventing venous thrombosis. However, adequate time must be available, as it is in elective surgery, to start therapy well before the operation.

These drugs oppose the action of vitamin K in the liver, thus blocking the synthesis of the plasma clotting factors, prothrombin and factors VII, IX and X. Studies in patients undergoing orthopedic surgery, such as reconstructive hip surgery, show a reduction in incidence of approximately 66% for DVT and 80% for PE, compared with controls.[14] Similar results have been reported for other types of surgery, as well as for heart disease. When used in patients with congestive heart failure, in which the risk of PE is high, oral anticoagulants reduced the incidence of DVT by 60% and of PE by 80% in comparison with that found in controls.[14]

The major drawback to the use of oral anticoagulants in surgically treated patients is the risk of massive hemorrhage intraoperatively and postoperatively. The incidence of such hemorrhage has been reported as high as 7%. This risk of hemorrhage and the need for strict laboratory control of the dosage have contributed to the relatively low level of use of these drugs for prevention of DVT in surgically treated patients. Warfarin is nonetheless used in patients at very high risk of having thrombosis; the bleeding complications are considered offset by warfarin's superior anticoagulant effectiveness.

Subcutaneous heparin: Low-dose subcutaneous heparin is a nearly ideal prophylactic agent against DVT in patients after surgery. It has no adverse effects and requires no special monitoring. Moreover, it produces no bleeding when used for clinical situations in which the patient is subjected to major trauma.

Heparin's anticoagulant effect has been shown to occur only in the presence of antithrombin, with which it combines to form an active complex that accelerates the blocking of the enzymatic action of thrombin. Small amounts of circulating heparin also neutralize activated factor X (and maybe also factors IX and XI) by enhancing antithrombin activity.

It has been shown that less heparin is required if hypercoagulability is treated with heparin before thrombin formation. Low-dose heparin administered after the thrombin formation stage may not be effective. Although there is no in vitro evidence that low-dose heparin can help dissolve thrombi, the reduced formation of thrombi in the presence of heparin may retard the activation of factor XIII fibrin-stabilizing factor. Furthermore, the loose network of fibrin formed under these circumstances

may be more susceptible to fibrinolysis or mechanical breakdown.

HEPARIN THERAPY IN PATIENTS AFTER SURGERY

Numerous studies involving a variety of postsurgical patients over the past few years have shown a significant reduction in the incidence of DVT in patients receiving heparin.[14] Heparin has also been found to be effective in reducing DVT in bedridden patients after myocardial infarction and stroke.[14] In a study by McCarthy et al[15] the incidence of DVT in 16 bedridden patients after acute stroke was 75% in the control group and 12.5% in the heparin-treated group.

There is less evidence of benefit in patients undergoing total hip replacement than in other surgically treated patients. In 1 study of hip-replacement patients, DVT occurred in 50% of the control group and in 20% of the heparin-treated group.[14] DVT may be due to extensive intimal damage resulting from torsion of the femoral vein during operation and consequent exposure of subintimal tissue to platelet adhesion and aggregation. Heparin has no known effect on platelets and is therefore ineffective in such cases.

In about 20% of surgically treated patients, thrombi develop that extend proximally from the calf vein into the popliteal, femoral or iliac veins. PE occurs in almost 50% of these patients. The effect of low-dose heparin on the extension of DVT has been evaluated in over 3,000 patients undergoing elective surgery.[14] Among 1,631 control patients, thrombi formed in 380, and extension occurred in 99, an incidence of 6.0%. In the low-dose heparin-treated group of 1,485 patients, thrombi were detected in only 95, and extension occurred in only 9 (0.6%) of these.

Does low-dose heparin prevent fatal and nonfatal PE? The largest and most important study to examine this outcome was the International Multicenter Trial,[16,17] conducted in 28 centers. This study enrolled 4,121 patients older than age 40 years undergoing various elective major surgical procedures. Of 180 patients who died postoperatively, 100 were in the control group and 80 in the heparin-treated group. Autopsies performed on 72 controls and 53 heparin-treated patients showed massive PE in 16 controls and in only 2 heparin-treated patients. In addition, 24 patients in the control group and 8 patients in the heparin group were treated for nonfatal PE; the difference in the 2 groups is again significant ($p < 0.005$).

The concept of administering low-dose subcutaneous heparin adjusted to clotting time evolved in the early 1960s. Despite evidence that this approach offered improved DVT prophylaxis, the additional laboratory work required discouraged its adoption.

This approach has recently been evaluated in several studies. In 1 study[18] of 79 patients who had undergone total hip replacement, the heparin dosage was increased when the 6-hour postinjection activated partial thromboplastin time (APTT) was less than 31.5 seconds, and was later decreased when this value increased to more than 36 seconds. DVT developed in 39% of patients who received fixed-dose heparin and in 13% of patients who received adjusted doses. Monitoring of the adjusted-dosage group showed that increasing doses were required throughout the first postoperative week in order to maintain the APTT within the designated range. This finding suggests that hip replacement surgery, which requires extensive tissue dissection, induces a hypercoagulable state that requires increasingly higher doses of heparin to prevent DVT. However, these findings await corroboration.

Combining stasis prevention with anticoagulation: Since both venous stasis and changes in blood coagulation are considered important in the pathogenesis of DVT, 2 approaches that address both factors have been tried.

The first approach, low-dose heparin plus compression stockings, has been shown to be more effective than heparin alone in patients undergoing abdominal surgery.[19]

The second approach combines heparin and dihydroergotamine (DHE), a potent vasoconstrictor that appears to act on the capacitance vessels of the limbs to increase venous blood flow. DHE also increases prostaglandin synthesis and may thus affect platelet function. Furthermore, DHE may increase fibrinolytic activity through increased release of plasminogen. Numerous randomized clinical trials of this combination have shown that the addition of DHE reduces by a further 50% the already reduced incidence of DVT in heparin-treated patients.

Low-molecular-weight heparin: Inhibition of plasma factor Xa by heparin increases with the drug's decreasing molecular weight. Several studies have evaluated the use of low-molecular-weight heparin to prevent DVT. In 1 such study, DVT developed in 7.5% of the patients receiving 5,000 APTT units of unfractionated heparin twice daily, and in only 2.5% of those receiving 1,850 APTT units of low-molecular-weight heparin. No significant differences were observed between the 2 groups in blood loss, postoperative drainage or formation of wound hematoma. Similar results have now been reported in 15 other studies.

Risk of hemorrhage: Hemorrhage risk is the main limitation of routine use of subcutaneous anticoagulants for DVT prophylaxis in surgically treated patients. The frequency of wound hematoma formation is a criterion for evaluating the risk of bleeding. Studies that have evaluated it have shown a higher risk during an 8-hour regimen, but not during a 12-hour regimen.[16,20–22]

A higher incidence of bleeding has been observed in some United States studies. This greater bleeding probably occurs because heparin in the United States is calibrated to the USP unit, which is 6 to 7% more potent than the international unit used by European manufacturers. Another possible reason for excessive bleeding is the use of multidose vials, which can lead to accidental overdosage. (Ampules of 5,000 units made for prophylactic use are now available.) Furthermore, sodium and calcium salts of heparin behave differently, with significantly less ecchymosis at the site of injection when calcium salts are used.

The risk of bleeding is minimized by careful patient selection, recognizing coexistent systemic or local abnor-

malities, and avoiding other drugs that cause bleeding. Contraindications to heparin prophylaxis include hemorrhagic disease, endocarditis, ulcers of internal organs, damage to the renal parenchyma, or hypertension (>200/120 mm Hg). Patients undergoing eye or central nervous system surgery, or in whom spinal anesthetics will be used, should not receive heparin prophylaxis.

Cautions pertaining to the risk of hemorrhage with subcutaneous heparin and the contraindications to its administration are summaried in Table I.

Semisynthetic heparin analog: A semisynthetic analog of heparin isolated from the respiratory tract of cattle has been shown to be approximately 3 times more active than heparin in potentiating anti-Xa factor in vivo.[23,24] Parenteral injection releases anti-Xa and lipoprotein lipase activity and platelet factor 4 antigen.[25] It has been suggested that the analog may act primarily by releasing heparin sulfate, present on endothelial cell surfaces.

In a comparative study[26] of 200 patients older than age 40 years undergoing abdominal surgery, DVT developed in 12.5% of the group receiving heparin, compared with only 6.3% of those receiving the synthetic. Bleeding was not significantly different between the 2 groups.

DEEP VEIN THROMBOSIS IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

The incidence of DVT in patients with acute MI ranges from 17 to 38%, similar to the incidence in surgically treated patients. The incidence is higher in patients with heart failure and those with shock and prolonged immobility and is probably also higher in older patients.

In 1 trial, clinically obvious PE occurred in 5% of patients who were not treated with anticoagulants.[27] In 3 randomized trials, low-dose heparin begun within 12 to 18 hours of the onset of symptoms of myocardial infarction, and continued for about 10 days, reduced the incidence of DVT to 4%, compared with 23% in untreated controls.[28–30]

Early mobilization is the main tactic for preventing DVT and PE in patients with acute myocardial infarction. High-risk patients (older than age 70 years, with large infarctions, previous history of myocardial infarction, in heart failure or shock, or requiring more than 3 days' immobilization) should receive immediate low-dose heparin followed by warfarin maintenance therapy.

TREATMENT OF DEEP VEIN THROMBOSIS

The treatment of DVT should prevent extension of the thrombus, prevent PE, and protect against the postphlebitic syndrome. Anticoagulant therapy with heparin followed by warfarin, with or without compression stockings, is warranted in patients with thrombi extending above the popliteal vein and in symptomatic calf-vein thrombosis.

Patients with superficial thrombophlebitis do not require anticoagulant therapy; they can usually be treated effectively with nonsteroidal anti-inflammatory drugs.

Heparin therapy is generally maintained for 7 to 10 days. A shorter course may be sufficient in patients with a remediable thrombus-provoking factor; but patients with large thrombi or a persistent predisposing factor, such as cancer, may require a longer course of heparin to interrupt the thrombotic process.

TABLE I Heparin Complications and Contraindications

Hemorrhage main complication
United States heparin 6 to 7% more potent than European
Multidose vials increase risk of overdose
Less ecchymosis when calcium salt of heparin used
Contraindicated for: hemorrhagic disease, endocarditis, internal organ ulcers, damaged renal parenchyma, hypertension (>200/120 mm Hg)
Contraindicated in eye or central nervous system surgery, and with use of spinal anesthetics

TABLE II Incidence of Hemorrhagic Complication Correlated with Intensity of Warfarin Therapy

PT 1.5–2.0 × control: 22% of warfarin patients
PT 1.25 × control: 4% of warfarin patients

PT = prothrombin time.

TABLE III Recommendations for the Treatment of Pulmonary Embolism

Treat immediately with heparin
Warfarin maintenance
Massive emboli, right-sided cardiac failure, hypotension require fibrinolytic therapy

To prevent recurrence of thrombosis after heparin therapy, continued full anticoagulation is needed. Oral warfarin is the drug of choice because of its superior effectiveness, and because oral administration is more convenient for the patient. In a prospective randomized study,[31] a 47% recurrence rate of DVT was observed within 3 months of proximal DVT diagnosis in patients receiving low-dose subcutaneous heparin, compared with no recurrence in the warfarin group. Although 3 months of oral anticoagulant therapy is generally recommended for uncomplicated venous thromboembolism or calf-vein thrombosis, patients with a persistent thrombotic predisposition or recurrent thrombosis may require up to 1 year of warfarin therapy.

In the past, the optimal therapeutic range of warfarin was based on a prothrombin time of 1.5 to 2.5 times the control value. However, early studies had been based on reagents with varying responsiveness to reduction in vitamin K-dependent coagulation factors.

In a randomized trial, Hull et al[32] compared the anticoagulant effectiveness and degree of bleeding caused by warfarin when the prothrombin time was maintained at 1.5 to 2.0 vs 1.25 times control. Hemorrhagic complications occurred in 22% of the higher-intensity group, compared with only 4% in the 1.25 times control group (Table II).

TREATMENT OF PULMONARY EMBOLISM

Recommended therapy for PE is summarized in Table III. Therapy for PE is generally the same as that for

DVT—immediate anticoagulation with heparin followed by warfarin maintenance. However, massive embolism, right-sided cardiac failure and hypotension are associated with a 30 to 40% hospital mortality rate and may require fibrinolytic therapy with urokinase or streptokinase. There is some evidence that these agents improve pulmonary perfusion, clot resolution and hemodynamic status, and also reduce the incidence of long-term effects. These agents are clearly indicated in patients who are severely compromised hemodynamically. However, their use in less severe cases must be weighed against their inconvenience and risks.

REFERENCES

1. Donaldson GA, Williams C, Schanez JG. A reappraisal of the application of the Trendelenburg operation to massive fatal embolism. *N Engl J Med 1963;268:171–174.*

2. Doran FSA, Drury M, Sivyen A. A simple way to combat the venous stasis which occurs in the lower limbs during surgical operations. *Br J Surg 1964; 51:486–490.*

3. Hills NH, Pflug JJ, Jeyasingh K, Boardman L, Calnan JS. Prevention of deep vein thrombosis by intermittent pneumatic compression of calf. *Br Med J 1972;1:131–135.*

4. Peterson J, Zucker MB. The effectof adenosine monophosphate, arcaine and anti-inflammatory agents on thrombosis and platelet function in rabbits. *Thrombosis et Diathesis Haemorrhagia 1970;23:148–158.*

5. Kelton JG, Hirsh J, Carter CJ, Buchanan MR. Thrombogenic effect of high dose aspirin in rabbits. Relationship to inhibition of vessel wall synthesis of prostaglandin I_2-like activity. *J Clin Invest 1978;62:892–895.*

6. Report of the steering committee on a trial sponsored by the Medical Research Council. Effect of aspirin on post-operative venous thrombosis. *Lancet 1972; 2:441–444.*

7. Encke A, Stock D, Danke HO. Doppelbindusie zur postoperativen thrombose prophylaxe mit dipyridamol Acetylsalicysaure. *Chir Scand 1976;47:670–673.*

8. Harris WH, Salzman EW, Athanasoulis CA, Waltman AC, DeSanctis RW. Aspirin prophylaxis of venous thromboembolism after total hip replacement. *N Engl J Med 1977;297:1246–1249.*

9. Zekert F, Kohn P, Vormittag E, Poigenfurst J, Thien M. Thromboembolieprophylaxe mit Acetylsalicylasure bei Operationen wegen jufgelenksnaher Frakturen. *Monatsschr Unfallheilkd 1974;77:97–110.*

10. Kline A, Hughes IE, Campbell H, Williams A, Zlosnick J, Leach KG. Dextran 70 in prophylaxis of thromboembolic disease after surgery—a clinically oriented randomised double blind trial. *Br Med J 1975;2:109–112.*

11. Gruber UF, Saldeen T, Brokop T, Eklof B, Eriksson I, Goldie I, Gran L, Hohl M, Jonsson T, Kristersson S, Ljungstrom KG, Lund T, Moe HM, Svensjo E. Incidence of fatal postoperative pulmonary embolism after prophylaxis with dextran 70 and low-dose heparin: an international multicentre study. *Br Med J 1980;280:69–72.*

12. Phil RB, Lemieux V. Comparison of effect of dipyridamole and adenosine on thrombus formation, platelet adhesiveness and blood pressure in rabbits and rats. *Nature 1968;218:1072–1074.*

13. Browse NL, Hall JH. Effect of dipyridamole on the incidence of clinically detectable deep vein thrombosis. *Lancet 1969;2:718–721.*

14. Kakkar VV. Prevention of venous thromboembolism. In: Bloom AL, Thomas DP, ed. Haemostasis and Thrombosis. *London: Churchill Livingstone, 1987:802–819.*

15. McCarthy ST, Robertson D, Turner JJ, Hawkey CT, Macey DJ. Low-dose heparin as a prophylaxis against deep-vein thrombosis after acute stroke. *Lancet 1977;2:800–801.*

16. International Multicentre Trial. Prevention of post-operative pulmonary embolism by low doses of heparin. *Lancet 1975;2:45–51.*

17. Kakkar VV. Efficacy of low-dose heparin in preventing post-operative fatal pulmonary embolism: results of an International Multicentre Trial. *DHEW Publication No. (NIH) 76N-866:207.*

18. Leyvraz PF, Richard J, Bachmann F, Van Melle G, Treyvaud JM, Livio JJ. Adjusted versus fixed-dose subcutaneous heparin in the prevention of deep-vein thrombosis after total hip replacement. *N Engl J Med 1983;309:954–958.*

19. Törngren S. Optimal regimen of low dose heparin prophylaxis in gastrointestinal surgery. *Acta Chirur Scand 1979;145:87–93.*

20. Gallus AS, Hirsh J, Tutle RJ, Trebilcock R, O'Brien SE, Carroll JJ, Minden JH. Small subcutaneous doses of heparin in the prevention of venous thrombosis. *N Engl J Med 1973;288:545–551.*

21. Kiil J, Axelsen F, Kiil J, Andersen D. Prophylaxis against post-operative pulmonary embolism and deep vein thrombosis by low-dose heparin. *Lancet 1978;1:1115–1116.*

22. Sagar S, Massey J, Sanderson JM. Low dose heparin prophylaxis against fatal pulmonary embolism. *Br Med J 1975;4:257–280.*

23. Lane DA, Michalski R, Van Ross ME, Kakkar VV. Comparison of heparin and a semi-synthetic heparin analogue A 73025.I. Kinetics of clearance from the circulation of man following intravenous injection. *Br J Haemotol 1977;37:239–245.*

24. Thomas DP, Lane DA, Michalski R, Johnson EA, Kakkar VV. A heparin analogue with specific action on antithrombin III. *Lancet 1977;1:120–122.*

25. Thomas DP, Merton RE, Barrowcliffe TW, Mulloy B, Johnson EA. Antifactor Xa activity of heparin sulfate. *Thromb Res 1979;14:501–506.*

26. Kakkar VV, Lawrence D, Bentley PG, de Haas HA, Ward VP, Scully MF. A comparative study of low doses of heparin and a heparin analogue in the prevention of post-operative deep vein thrombosis. *Thromb Res 1978;13:111–112.*

27. Veterans Administration Cooperative Clinical Trial. Anticoagulants in acute myocardial infarction. *JAMA 1973;225:726–729.*

28. Nicolaides AN, Kakkar VV, Renney JT, Kidner PH, Hutchinson DC, Clarke MB. Myocardial infarction and deep vein thrombosis. *Br Med J 1971;1:432–435.*

29. Warlow G, Terry G, Beattie AG, Ogston D, Douglas AS. A double-blind trial of low doses of subcutaneous heparin in the prevention of deep vein thrombosis after myocardial infarction. *Lancet 1973;2:936–937.*

30. Emerson PA, Marks P. Preventing thrombosis after myocardial infarction. *Br Med J 1977;1:18–21.*

31. Hyas TM, Hull RD, Weg JG. Antithrombotic therapy for venous thromboembolism disease. *Chest 1986;89:suppl:26S–35S.*

32. Hull R, Hirsch J, Jay R, Carter C, England C, Gent M, Turpie AG, McLoughlin D, Dodd P, Thomas M, Raskob G, Ockelford P. Different intensities of oral anticoagulant therapy in the treatment of proximal vein thrombosis. *N Engl J Med 1982;307:1676–1681.*

13.12-9

The American Journal of Cardiology

FEBRUARY 20, 1990

A Symposium: Pharmacologic Management of Ventricular Arrhythmias — Current Status in the Role of Moricizine HCl

GUEST EDITORS:

Joel Morganroth, MD
Director, Center of Excellence for Cardiovascular Studies
The Graduate Health System
Clinical Professor of Medicine
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

J. Thomas Bigger, Jr., MD
Director, Arrhythmia Control Unit
Columbia Presbyterian Medical Center
Professor of Medicine & Pharmacology
Columbia University
New York, New York

A YORKE MEDICAL JOURNAL/CAHNERS PUBLISHING COMPANY

The American Journal of Cardiology

FEBRUARY 20, 1990 VOL. 65 NO. 8

A Symposium: Pharmacologic Management of Ventricular Arrhythmias — Current Status in the Role of Moricizine HCl

GUEST EDITORS:

Joel Morganroth, MD
Director, Center of Excellence for Cardiovascular Studies
The Graduate Health System
Clinical Professor of Medicine
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

J. Thomas Bigger, Jr., MD
Director, Arrhythmia Control Unit
Columbia Presbyterian Medical Center
Professor of Medicine & Pharmacology
Columbia University
New York, New York

This symposium was held October 19–22, 1989, in Scottsdale, Arizona, and was supported by an educational grant from Du Pont Pharmaceuticals.

EDITOR-IN-CHIEF
William C. Roberts, MD

MANAGING EDITOR, SPECIAL PROJECTS
Judith Wagner

PUBLISHER, SPECIAL PROJECTS
Kenton T. Finch

PRODUCTION EDITOR
Joan Gunning

PROOF EDITOR
Mary Crowell

THE AMERICAN JOURNAL OF CARDIOLOGY.® (ISSN 0002-9149) February 20, 1990, Vol. 65, No. 8 (USPS: 505–750).

Member, American Business Press, Inc. and Audit Bureau of Circulations. Published 4 times in January, February, June, July, September and October, 3 times in March, April, May, August and November, and 2 times in December, by The Cahners Publishing Company, a Division of Reed Publishing USA, 275 Washington St., Newton, MA 02158-1630. Terrence M. McDermott, President; Jerry D. Neth, Vice President/Publishing Operations; J.J. Walsh, Financial Vice President/Magazine Division; Thomas J. Dellamaria, Vice President/Production and Manufacturing.

SUBSCRIPTIONS: Sollcited only from cardiologists and other physicians. Publisher reserves the right to refuse unqualified subscribers. Subscribers agree that no article or any part thereof published in any editions of the American Journal of Cardiology received under this subscription agreement may be copied, recorded or reproduced in any form or by any means, electronic or mechanical, including, among other things, photocopying or the storing of part or all of such articles on any information retrieval system, without the written permission of the Publisher. Address correspondence regarding subscriptions and changes of address to: THE AMERICAN JOURNAL OF CARDIOLOGY, 44 Cook Street, Denver, Colorado 80206-5800 (1-800-637-6073). Please include your zip code and, in case of change of address, copy of old address label. Changes of address must reach the Journal one month preceding month of issue. Single copy price: Regular issues $10.00; Symposium and special issues $12.00. Subscription rate for individuals in field of publication: United States 1 year $66, 2 years $112, 3 years $158; Canada and all other countries 1 year $105, 2 years $178, 3 years $252; Residents and Medical Students: United States 1 year $33; Canada & all other countries 1 year $85. Institutions: United States 1 year $95, 2 years $162, 3 years $228; Canada & all other countries 1 year $125, 2 years $213, 3 years $300. Air Mail available at additional charge of $150 per year. The Journal is not responsible for replacing missing issues unless the Circulation Department is notified of nonreceipt within 3 months of issue date.

Second class postage paid at Denver, CO, and at additional mailing office. Printed in U.S.A. Trademark™ in U.S. Patent Office. © Copyright 1990 by Reed Publishing USA: Saul Goldweitz, Chairman; Ronald G. Segel, President and Chief Executive Officer. All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording or by any information storage retrieval system, without permission of the copyright owner. Prices on bulk reprints of articles available on request.

The Publisher assumes no liability for any material published in the Journal. All statements are the responsibility of the authors.

MANUSCRIPTS: Address all manuscripts to William C. Roberts, MD, Editor-in-Chief, the American Journal of Cardiology, 7960 Old Georgetown Road, Suite 2C, Bethesda, Maryland 20814.

POSTMASTER: Send address changes to: The American Journal of Cardiology, 44 Cook Street, Denver, Colorado 80206-5800.

Cahners Publishing Company, A Division of Reed Publishing USA □ Specialized Business Magazines for Building & Construction □ Manufacturing □ Foodservice & Lodging □ Electronics & Computers □ Interior Design □ Printing □ Publishing □ Industrial Research & Technology □ Health Care □ Entertainment.

Publisher's Note

The opinions expressed in this presentation are those of the panelists and are not attributable to the sponsor or the publisher, editor, or editorial board of The American Journal of Cardiology. Clinical judgment must guide each physician in weighing the benefits of treatment against the risk of toxicity. References made in the articles may indicate uses of drugs at dosages, for periods of time, and in combinations not included in the current prescribing information.

Editor's suggestion: The symposium issues for a full year should be bound together separately from the regular issues.

CONTENTS

The American Journal of Cardiology

FEBRUARY 20, 1990 VOL. 65 NO. 8

A SYMPOSIUM: PHARMACOLOGIC MANAGEMENT OF VENTRICULAR ARRHYTHMIAS — CURRENT STATUS IN THE ROLE OF MORICIZINE HCl

1D
Overview: Moricizine — Can It Meet the Challenge?
Joel Morganroth and J. Thomas Bigger, Jr.

3D
Implications of the Cardiac Arrhythmia Suppression Trial for Antiarrhythmic Drug Treatment
J. Thomas Bigger, Jr.

11D
Clinical Development of Moricizine as an Antiarrhythmic Agent
Sara Armstrong Mahler and R. Michael Borland

15D
Cardiac Electrophysiologic Effects of Moricizine Hydrochloride
J. Thomas Bigger, Jr.

21D
Clinical Pharmacokinetics of Moricizine
Lyle A. Siddoway, Sorell L. Schwartz, Jean T. Barbey, and Raymond L. Woosley

26D
Dose Effect of Moricizine on Suppression of Ventricular Arrhythmias
Joel Morganroth

32D
Comparisons of Efficacy and Tolerance of Moricizine with Other Antiarrhythmic Agents in the Treatment of Chronic Ventricular Arrhythmias
Jeffrey L. Anderson

41D
Efficacy of Moricizine in Malignant Ventricular Arrhythmias
Leonard N. Horowitz

47D
Noncardiac Adverse Effects and Organ Toxicity of Moricizine During Short- and Long-Term Studies
Harold L. Kennedy

51D
Proarrhythmic Potential of Moricizine: Strengths and Limitations of a Data Base Analysis
Craig M. Pratt

56D
Antiarrhythmic Drug Therapy for Congestive Heart Failure with Focus on Moricizine
Philip J. Podrid and Scott L. Beau

65D
Placement of Moricizine in the Selection of Antiarrhythmic Drug Therapy
Joel Morganroth

68D
Discussion

The American Journal of Cardiology

Overview: Moricizine—Can It Meet the Challenge?

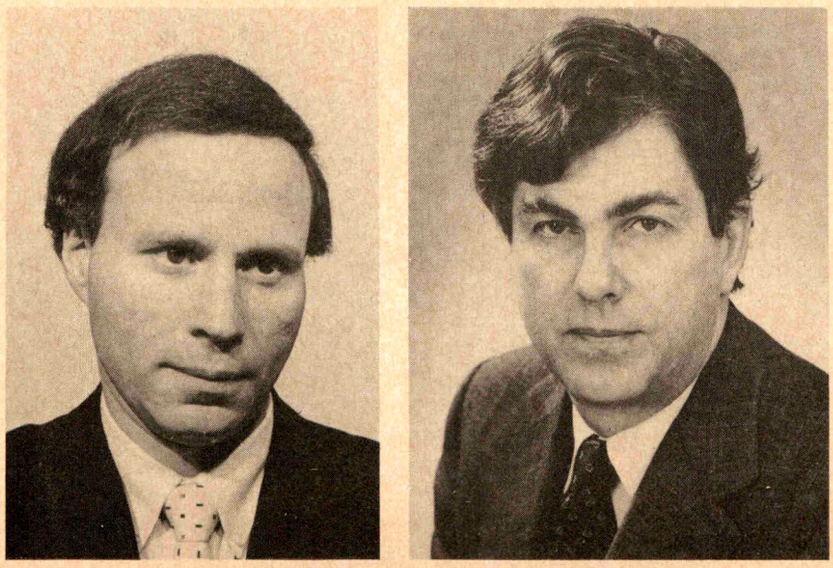
Joel Morganroth, MD, and J. Thomas Bigger, Jr., MD

Since April 1989, clinicians have been forced to reassess their management of patients with ventricular arrhythmias because of the unexpected preliminary findings reported from the Cardiac Arrhythmia Suppression Trial (CAST). Two drugs, encainide and flecainide, that were the most effective and best tolerated by patients with potentially malignant ventricular arrhythmias, are associated with a substantial increase in mortality in such patients after myocardial infarction. This surprising finding challenges prior concepts and recommendations in the use of antiarrhythmic drugs and substantially raises the stakes in the risk/benefit assessment of such therapy.

How will moricizine hydrochloride, a non "IC agent," which is one of the next drugs slated for approval in the United States, meet these challenges? Moricizine is a phenothiazine derivative synthesized in the Soviet Union in 1964. Du Pont licensed moricizine and began clinical trials in the mid-1970s pursuing only the indication for treatment of ventricular arrhythmias. Moricizine is a Vaughn Williams class I agent with a novel electrophysiologic profile. It undergoes rapid first-pass metabolism and has several active metabolites with long duration of actions. Moricizine is as effective as quinidine in suppressing spontaneous ventricular ectopy and unsustained ventricular tachycardia and more effective than propranolol and disopyramide, but less potent than encainide and flecainide.

Moricizine renders about 20% of patients with inducible sustained ventricular tachycardia noninducible comparable to most class I agents. Its most attractive features are its low rate of inducing proarrhythmia or congestive heart failure in all patient groups. Patients taking moricizine have a low rate of discontinuation from therapy because of noncardiac side effects. When discontinuation of therapy does occur, the principal symptoms are dizziness and nausea. Antiarrhythmic efficacy is maintained long-term in patients with or without left ventricular dysfunction.

Moricizine's unique electrophysiologic profile, reasonable efficacy, excellent tolerance profile and convenient dose schedule (3 to 2 times daily) makes it an



***Left,* Joel Morganroth, MD, and *right,* J. Thomas Bigger, MD**

attractive new antiarrhythmic drug. However, in the aftermath of the CAST our primary concern for any agent is its long-term safety. Fortunately, moricizine to date in the CAST has not raised any safety concerns. Its continuation in the CAST will uniquely provide us with enough long-term mortality data to establish its safety to an unprecedented degree.

In January 1989, the Food and Drug Administration's Cardiovascular and Renal Drugs Advisory Board recommended moricizine's approval for sustained ventricular tachycardia and symptomatic ventricular arrhythmias. It may well be that moricizine deserves consideration as first-line use for sustained ventricular tachycardia, and just after β-blocking therapy in the algorithm for drug selection in patients with debilitating symptoms from benign or potentially malignant ventricular arrhythmias. Availability of moricizine and data from ongoing studies will further define its role relative to other antiarrhythmic drugs.

Implications of the Cardiac Arrhythmia Suppression Trial for Antiarrhythmic Drug Treatment

J. Thomas Bigger, Jr., MD

The Cardiac Arrhythmia Suppression Trial (CAST) is a randomized, placebo-controlled, double-blind, multicenter clinical trial involving 27 centers and more than 100 hospitals in North America and Europe to test the 1-tailed hypothesis that suppression of ventricular arrhythmias in patients with left ventricular dysfunction after myocardial infarction will reduce arrhythmic death. Since April 18, 1989, the CAST is enrolling patients aged <80 years with ≥6 ventricular premature complexes and left ventricular ejection fraction ≤40%. Sustained ventricular tachycardia, class IV congestive heart failure or class IV angina pectoris are exclusion criteria. During a prerandomization period, antiarrhythmic drugs are titrated to suppress ventricular arrhythmias. If ≥80% suppression is achieved during open-label titration, patients are randomized to the effective dose or to a matched placebo. If only partial suppression (1 to 79%) is achieved, patients are eligible for a substudy that randomizes them to the best dose found during open-label titration or to placebo. The only patients not randomized to treatment are those with increased arrhythmias or drug intolerance during titration. On April 18, 1989, encainide and flecainide were removed from the CAST because these drugs increased the death rate 2.5-fold. There were no imbalances in baseline risk variables between the encainide/flecainide group and the placebo group that might explain the adverse treatment effect. There was remarkable uniformity of the adverse effect across all subgroups. There were no subgroups that benefited from treatment; all were either harmed or not evaluable. Moricizine was continued in the CAST because it has a significant chance of showing benefit. The CAST still has the opportunity to make a major impact on the future management of asymptomatic or minimally symptomatic ventricular arrhythmias after myocardial infarction by determining whether prophylaxis or treatment of symptomatic arrhythmias is the appropriate approach. Enrollment for the CAST is actively underway and physicians are encouraged to recommend participation.

(Am J Cardiol 1990;65:3D–10D)

It is useful to publish a body of accumulated information about a drug near the time of its launch to provide a critical mass of authoritative information in one readily accessible place. Our review of moricizine in this symposium is complicated by the fact that concepts about antiarrhythmic drugs are changing rapidly as a result of preliminary findings for encainide and flecainide in the Cardiac Arrhythmia Suppression Trial (CAST). Before we begin the review of the important information learned about moricizine during its long development period, it will be useful to review the CAST preliminary results and their implications for clinical practice and to have some general discussion about the impact of the preliminary CAST results on future antiarrhythmic drug use and development.

On August 10, 1989, the preliminary findings of the CAST were published in *The New England Journal of Medicine*.[1] The results were terse and factual. In the same issue of the journal, an editorial by Ruskin[2] discussed the implications of the findings. Since that time, there have been a number of meetings to discuss the CAST preliminary results. The Working Group on Arrhythmias of the European Society of Cardiology met on October 1 and 2, 1989, in Sardinia. Representatives from the common market countries met with a group of 6 American arrhythmia experts to discuss the implications of the CAST results. Two CAST investigators, Thomas Bigger and Raymond Woosley, were invited to provide information for the participants. The conclusions by the Working Group on Arrhythmias about the CAST results will be published jointly in *The European Journal of Cardiology* and in *Circulation*. The Food and Drug Administration (FDA) had a session on October 5 to review CAST results and discuss their implications for drug development. The opinion of the Cardiovascular and Renal Drugs Advisory Board to the FDA was summarized by Pratt et al.[3] The National Institutes of Health is conducting a workshop in January 1990 to review the CAST findings and discuss how to use them as a platform for

From the Division of Cardiology, Department of Medicine, Columbia University, New York, New York 10032. This study was supported in part by National Institutes of Health Contract HC-65048 from the National Heart, Lung, and Blood Institute, and by Grant RR-00645 from the Research Resources Administration, Bethesda, MD; and by funds from The Milstein Family Foundation, The Dover Foundation, George and Abby O'Neill, Robert Winthrop, and the Shirlee and Henry Benach Foundation, New York, New York.

Address for reprints: J. Thomas Bigger, Jr., MD, Arrhythmia Control Unit, Columbia-Presbyterian Medical Center, 630 West 168th Street, New York, New York 10032.

TABLE I Determinants of Sample Size for CAST

Average follow up	3 years
Arrhythmic death	11% per 3 years
Treatment effect	30% reduction in arrhythmic death
Type I (α) error	0.025 1-tail hypothesis
Type II (β) error	0.15
Drop-out rate	30% (20% in first year, then 5% per year)
Drop-in rate	6% (2% per year)

CAST = Cardiac Arrhythmia Suppression Trial.

future institute- or investigator-initiated research. Also, the CAST investigators and the sponsors of encainide and flecainide have continued to analyze the CAST data base to gain a better understanding of the preliminary findings.

What is the principal objective of the CAST? The CAST is a randomized, placebo-controlled, double-blind, international, multicenter clinical trial that began enrollment in June 1987 to test the 1-tailed hypothesis that suppression of ventricular arrhythmias after myocardial infarction with long-term antiarrhythmic drug treatment will reduce arrhythmic death by 30% or more.[1] Twenty-seven centers and more than 100 hospitals in 3 countries, the United States, Canada and Sweden, are participating. Enrollment will continue for 3 or 4 years (from 1987 to 1991) and follow-up for 2 to 5 years (until 1994).

Who is eligible for the CAST? Before April 18, 1989, survivors of myocardial infarction who were aged <80 years and had ≥6 ventricular premature complexes per hour on a 24-hour continuous electrocardiographic recording obtained between 6 days and 2 years after myocardial infarction were eligible for the CAST. For patients enrolled between 6 and 90 days after infarction, a left ventricular ejection fraction ≤55% was required; for patients enrolled ≥90 days after the onset of myocardial infarction, left ventricular ejection fraction ≤40% was required. After April 18, 1989, the enrollment window was restricted to within 90 days and left ventricular ejection fraction criterion was reduced to ≤40%.

What was the rationale for the two ejection fraction criteria? The purpose of 2 ejection fraction criteria was to equalize the risk of death early and late after myocardial infarction. In the Cardiac Arrhythmia Pilot Study (CAPS), which had a 6- to 60-day enrollment window, it was found that the incidence of death or sustained arrhythmic events was very low in patients with left ventricular ejection fractions ≥55% (i.e., the upper quartile of the ejection fraction distribution). Therefore, it was decided to exclude patients with left ventricular ejection fractions ≥55% in the 6- to 90-day window, as having an overall risk of arrhythmic events too low to achieve a risk/benefit ratio sufficient to enroll in the CAST. For patients enrolled from 90 days to 2 years after infarction, left ventricular ejection fraction ceiling was set at 40% in order to match the expected event rates between patients enrolled early (6 to 90 days) and late (90 days to 2 years) after myocardial infarction. This strategy worked very well. The patients enrolled before and after 90 days had almost identical mortality rates.

Who is excluded from the CAST? Patients with sustained ventricular tachycardia are excluded from the CAST. Also, patients are excluded who, at the time of enrollment, have New York Heart Association class IV congestive heart failure or Canadian cardiovascular class IV angina pectoris.

What is the design of the CAST? The design of the CAST is uniquely suitable for testing the 1-tailed suppression hypothesis (see Fig. 1). The original parameters for the CAST sample size computation are given in Table I. During an open-label drug treatment period, suppression of ventricular arrhythmias is sought by titrating antiarrhythmic drugs. If ≥80% suppression of ventricular premature complexes is achieved during open-label titration and the effective drug is well tolerated, patients are randomized in the main study to the therapy found during open-label titration or to a matched placebo. If partial suppression (1 to 79%) is achieved, patients are eligible for a substudy that randomizes them to the best therapy found during open-label titration or to a matching placebo. Patients who have an increase in frequency of ventricular premature complexes, cannot tolerate any of the drugs, die, or decide to discontinue treatment are the only ones not randomized to treatment. As of April 18, 1989, the last day encainide and flecainide were in the CAST, 76% of those who signed a consent form were randomized to the main study, 6% were randomized to the substudy for those who had partial suppression, and 18% were not randomized (Fig. 1).

How was open-label drug/dose titration conducted? Before April 18, 1989, 3 active drugs were used in a number of randomly assigned sequences (Fig. 2). For patients with an ejection fraction ≥30%, the sequence contained all 3 drugs. For patients with left ventricular ejection fraction <30%, only 2 drugs, encainide and moricizine, were administered. Patients were randomly assigned to start therapy with encainide or moricizine first. Each drug had 2 dose levels (see Table II), the same as the 2 lower doses used in CAPS, and dosing always proceeded from the low to the high dose. After April 18, 1989, only moricizine remained in the CAST and, based on dose-response information from the Du Pont New Drug Application data base, a third dose (900 mg) was added to the titration sequence.

How is randomization conducted? Before April 18, 1989, randomization was stratified on: (1) clinical center; (2) left ventricular ejection fraction ≥30 or <30%; and (3) time of enrollment, 6 to 90 days or ≥90 days to 2 years. Randomization to blinded treatment with drug or placebo began the main trial or the substudy for partially suppressed patients. After April 18, 1989, randomization was stratified only on enrolling center and ejection fraction since the enrolling window was shortened.

Why were encainide and flecainide removed from CAST? The CAST protocol permits drugs to be removed from or added to the trial. On April 17, 1989, the Data and Safety Monitoring Board held its regular semiannual meeting, reviewed mortality data complete as of March 30, 1989, and recommended that encainide and flecainide be removed from the CAST because it had become

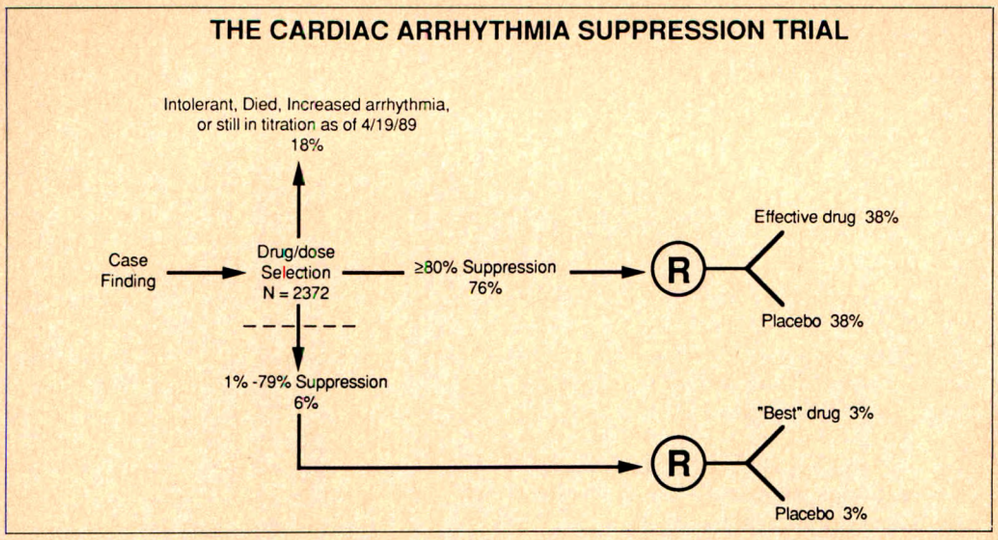


FIGURE 1. The design of the Cardiac Arrhythmia Suppression Trial (CAST). The numbers indicate the patient flow in the CAST up to the day encainide and flecainide were removed from the trial, i.e., April 18, 1989.

virtually impossible to establish any beneficial effect from these drugs if they were continued to the end of study and because of strong evidence that these drugs increased the death rate compared with placebo. The Data and Safety Monitoring Board also recommended that moricizine be continued in the CAST because it still has a significant chance of showing benefit and that other antiarrhythmic drugs be reviewed as possible additions to the CAST. The National Heart, Lung, and Blood Institute accepted the recommendation that same day. On April 18, 1989, a message was sent to each CAST clinical center to discontinue treatment in all patients who had been assigned to encainide, flecainide, or their corresponding placebos.

How much did encainide and flecainide increase the mortality rate in CAST? The data reviewed by the Data and Safety Monitoring Board on April 17, 1989, had a cutoff date of March 30, 1989. At that time, 730 patients had been randomized to encainide or flecainide and 725 to a corresponding placebo.[1] With an average of about 300 days of exposure to CAST treatment, there were 78 deaths (n = 70) or nonfatal cardiac arrests (n = 8) in the group treated with encainide, flecainide, or with the corresponding placebos (event rate 5.4%). Of the 78 events, 54% were primary arrhythmic events. The primary end point for the trial, arrhythmic death or nonfatal cardiac arrest, was experienced by 4.5% of the patients randomized to encainide or flecainide compared with 1.2% of the patients randomized to placebo. All of the 8 nonfatal cardiac arrests occurred in the active treatment group. Patients taking encainide or flecainide were 3.6 times as likely to experience arrhythmic death or nonfatal cardiac arrest as those treated with placebo. The chance of experiencing death of any cause or cardiac arrest was 7.7% in patients treated with encainide or flecainide compared with 3.0% for placebo, an increase in risk of 2.5. There was no difference for noncardiac deaths between the placebo and active treatment groups. The mortality events up to April 18, 1989, when encainide and flecainide were removed from the CAST, are listed in Table III. At this time, the average exposure time was less than 1 year. The

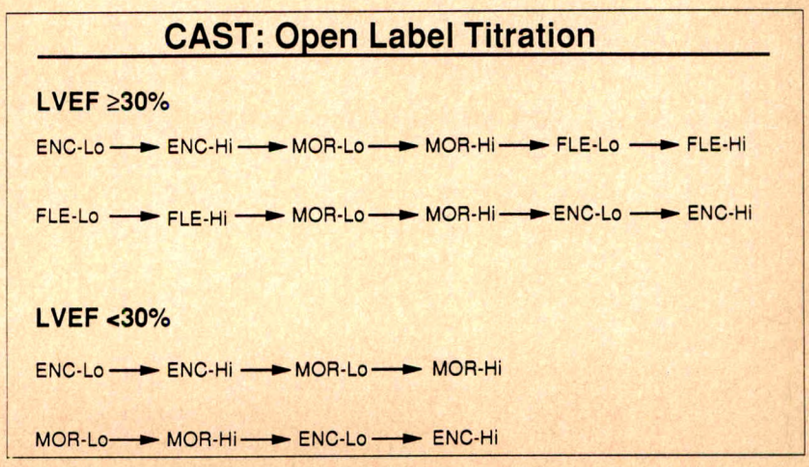


FIGURE 2. The randomization scheme for the phase of the Cardiac Arrhythmia Suppression Trial (CAST) before encainide (ENC) and flecainide (FLE) were removed from the trial. LVEF = left ventricular ejection fraction; MOR = moricizine.

TABLE II Doses of Drugs Used in CAST

Drug	Dose (mg)	
	Low	High
Encainide	35 TID	50 TID
Flecainide	100 BID	150 BID
Moricizine	200 TID	250 TID

BID = 2 times a day; CAST = Cardiac Arrhythmia Suppression Trial; TID = 3 times a day.

values in this table represent an update to those in the article in *The New England Journal of Medicine*. Ten additional deaths are recorded and some of the classifications have changed. The overall result is, of course, unchanged.

Could baseline differences at the time of randomization account for the higher mortality rate in the active treatment group than in the control group? There were no imbalances between the group treated with encainide or flecainide and the group treated with placebo with respect to baseline risk variables that might confound the apparent adverse treatment effect. Age, history of previous infarction, angina pectoris, congestive heart failure, hypertension, diabetes, sustained arrhythmias, baseline left ventricular ejection fraction, ventricular arrhythmia frequency, electrocardiographic intervals, therapy in hospital and discharge medications all were closely matched in patients randomized to encainide or flecainide and those randomized to placebo. Also, almost 90% of the patients who died or experienced a nonfatal cardiac arrest were taking their assigned study medication at the time of the event.

Did any subgroups benefit from encainide or flecainide treatment? The increase in death rate for patients treated with encainide or flecainide was observed consistently in the various subgroups within the study (i.e., there was no interaction between treatment and age, time from myocardial infarction to enrollment, left ventricular ejection fraction, baseline ventricular arrhythmia frequency, baseline QRS duration, or the use of digitalis, diuretics, β blockers or calcium channel blockers). The relative risk of dying or experiencing a nonfatal cardiac arrest was almost identical for both drugs (2.3 for encainide and 2.7 for flecainide), although the absolute mortality rate was lower for flecainide and its corresponding placebo because patients with left ventricular ejection fraction <30% were not randomized to flecainide. Thus, there was remarkable uniformity of treatment effect across all subgroups. There were no subgroups that benefited from treatment; all were either harmed or not evaluable.

TABLE III Deaths and Cardiac Arrests in 1,498 Patients Randomized to Encainide/Flecainide or to Placebo (Before April 18, 1989)

Type of Death	Encainide/ Flecainide (n = 755)	Placebo (n = 743)
Arrhythmic or cardiac arrest	43	16
Other cardiac death	16	5
Noncardiac	3	5
Total (deaths and cardiac arrest)	62	26

Average exposure: encainide/flecainide, 302 days; placebo, 311 days.

Why weren't we aware of this adverse effect before? The CAST findings point out the need for large-scale controlled clinical trials for long-term safety assessment of drugs. The modest-sized controlled studies performed by drug companies before FDA approval usually do not have the power to detect a mortality effect, even one as large as that found in the CAST. Also, there is no way that the harmful effects of encainide and flecainide could be detected in uncontrolled clinical use because there is no comparison group in this setting. For the public safety, for our patients, and for physicians who treat patients we must have this kind of knowledge. There is only one way to get it and that's controlled clinical trials. Not only are drug development programs too small to detect adverse effects on mortality, but also patients with recent myocardial infarction often are excluded from premarketing antiarrhythmic drug trials.

Are there subgroups of patients with ventricular arrhythmias after myocardial infarction who might benefit from encainide or flecainide treatment? First, all patients in the CAST who could be treated with antiarrhythmic drugs were treated so that no subgroups were excluded. The CAST protocol simulates the way antiarrhythmic drugs are used during conventional treatment of postinfarction ventricular arrhythmias. Patients with ventricular arrhythmia and left ventricular dysfunction were selected for treatment and those whose arrhythmias were suppressed by ≥1% were followed with treatment in the main study or the substudy for patients with partial suppression; 82% of the patients who had qualifying arrhythmias and were enrolled in the study were randomized and treated. The only patients who were not treated and followed were those who died during titration, had no arrhythmia suppression, or could not tolerate any study drug and dose available in the titration strategy. It is unlikely that such patients could be treated in a practice setting. Second, there were no subgroups that benefited from treatment. Patients with higher mortality rates, e.g., older patients, patients with severely depressed left ventricular function, and those with higher arrhythmia frequency or complexity were harmed as much as groups with lower mortality rates. Therefore, the CAST results are relevant to clinical practice and there are no groups that seem to have a chance of benefit from treatment with encainide or flecainide.

What is the mechanism of the increased mortality in postinfarction patients treated with encainide or flecainide? The mechanism of the increased mortality in the patients treated with encainide or flecainide in the CAST is not known. Ruskin[2] speculated that the deaths might be due to aggravation of ventricular arrhythmias. The higher relative risk in the encainide/flecainide group for sudden cardiac death/cardiac arrest than for total or

noncardiac death suggests that arrhythmic deaths were increased by treatment with these 2 drugs.[1] However, several features of the mortality findings in the CAST are different from those previously described for proarrhythmic effects. First, the increased mortality occurred despite marked suppression in the frequency of ventricular premature complexes and episodes of unsustained ventricular tachycardia. Second, the survival curves for patients treated with encainide/flecainide and the corresponding placebo group continue to separate over the 300 days of follow-up reported by CAST.[1] Current concepts of proarrhythmia predict that the frequency of ventricular premature complexes and unsustained ventricular tachycardia will increase when patients experience proarrhythmia.[4,5] Also, proarrhythmic events are expected to concentrate in the first 30 to 60 days after starting treatment.[6–8] Current concepts about proarrhythmia may be incomplete and biased by what is easy to observe and recognize. Encainide or flecainide might exert their adverse effect on mortality by: (1) making sustained, reentrant ventricular arrhythmias more likely by increasing the relative infarct size, (2) depressing left ventricular function, (3) increasing ischemia, or (4) increasing the likelihood of fatal ventricular arrhythmias during ischemia or periods of increased sympathetic nervous system activity.

Flecainide can cause inducible, sustained ventricular arrhythmia in dogs that have subacute myocardial infarction but are not inducible without the drug.[9,10] Flecainide slows conduction around infarcted tissue so that the conduction path is lengthened and sustained ventricular tachycardia is easier to induce.[11] Also, flecainide does not increase the electrical ventricular fibrillation threshold.[12]

Flecainide has been noted to aggravate left ventricular dysfunction, especially in patients with preexisting congestive heart failure or in those with left ventricular ejection fraction <30%, or both.[13] More recently, encainide has also been implicated.[14,15] Encainide and flecainide could increase mortality by aggravating left ventricular dysfunction per se. Also, these drugs could increase myocardial ischemia and the likelihood of sudden cardiac death by depressing left ventricular function and thereby increasing myocardial oxygen demand.

Encainide and flecainide could increase the likelihood of malignant ventricular arrhythmias during myocardial ischemia. Flecainide increases the probability of ventricular fibrillation during ischemia in dogs with previous myocardial infarction.[10,11] In the same model, β-adrenergic blocking drugs (class II action) and amiodarone or sotalol (class III action) were protective (i.e., the model discriminates among antiarrhythmic drugs.[16–18]) The effect of encainide or flecainide treatment on the likelihood of ventricular fibrillation during increased sympathetic nervous activity in animals with previous myocardial infarction has not been explored. Recent reports of sustained ventricular tachycardia or ventricular fibrillation occurring during exercise testing during treatment with encainide or flecainide suggest an interaction with exercise variables, e.g., heart rate, ischemia, or increased sympathetic nervous system activity, that can provoke malignant ventricular arrhythmias.[14,15,19,20]

Our working hypothesis to explain the increased mortality in the CAST encainide/flecainide groups is an adverse interaction between these drugs and myocardial ischemia that promotes ventricular fibrillation. Some of the encainide/flecainide associated deaths may be due to ventricular tachycardia promoted by drug-induced conduction slowing. It appears unlikely that the latter mechanism accounts for many of the drug-associated deaths. Otherwise, there should have been a higher relative risk of nonfatal, sustained ventricular tachycardia in the encainide/flecainide treated groups.

Do the CAST results apply to other drugs with class I antiarrhythmic action? May et al[21] and Furberg[22] reviewed clinical trials of antiarrhythmic drug therapy after myocardial infarction when 100 or more patients were studied, patients were randomized to treatment or control groups, and all-cause mortality was reported. No overall trend suggesting benefit was found in 8 long-term postinfarction antiarrhythmic drug trials, 6 of which studied antiarrhythmic drugs with class IB action (i.e., phenytoin, tocainide or mexiletine) and 2 others that studied aprindine. Three of the studies had almost identical mortality rates in the control and active treatment groups, 3 studies showed a mortality rate that was 32 to 58% higher in the group treated with antiarrhythmic drugs, and the 2 aprindine studies, which only enrolled patients who had ventricular arrhythmias and attempted to suppress ventricular arrhythmias by dose ranging, showed a 40 and 23% lower mortality rate in the aprindine-treated patients.[21,22] The results of these 8 small studies fail to suggest any benefit of treatment with antiarrhythmic drugs in unselected patients after myocardial infarction. Hine et al[23] performed a meta-analysis of these studies and found a statistically significant increase in mortality rate. The overall odds ratio for patients dying with active treatment vs placebo was 1.38 (95% confidence interval 1.09 to 1.74). These workers concluded that treatment of unselected patients at moderate risk of sudden cardiac death after myocardial infarction with drugs that have class I antiarrhythmic action is unwarranted. Recently, Coplen et al[24] conducted a meta-analysis of 6 trials that evaluated the safety and efficacy of quinidine for maintaining sinus rhythm after cardioversion for chronic atrial fibrillation. Although the probability of sustaining sinus rhythm for a year was doubled in the quinidine-treated group (50 vs 25%), the probability of dying was quadrupled in the quinidine-treated group (2.7 vs 0.6%). Although only about 16% of the 800 patients evaluated had coronary heart disease, 88% had structural heart disease of some kind. Thus, there are discouraging results for antiarrhythmic drugs with class IA, IB and IC action. The only encouraging results are for aprindine and moricizine, 2 drugs with class I action but with other special features. By virtue of use in the CAPS and CAST, moricizine has the largest body of controlled safety information of any drug with class I action for use against ventric-

ular arrhythmias after myocardial infarction. With what is currently known, it would not be prudent to treat asymptomatic or minimally symptomatic ventricular arrhythmias after myocardial infarction with any conventional drugs with class I antiarrhythmic action.

What about drugs with other classes of antiarrhythmic action? Drugs with class II antiarrhythmic action (β blockade) have been shown to reduce arrhythmias after myocardial infarction and to decrease mortality.[25] The effect on mortality is larger in patients who have arrhythmias or left ventricular dysfunction before treatment, and arrhythmic or sudden death is reduced more strikingly than total mortality. The effect of drugs with class III antiarrhythmic action (those that prolong cardiac action potentials) on patients with postinfarction ventricular arrhythmias and mortality is not known. Several clinical trials are underway to determine whether amiodarone will improve survival after myocardial infarction. Drugs with class IV antiarrhythmic action (those that block calcium channels) have no significant effect on spontaneous ventricular arrhythmias after myocardial infarction[26] and no effect on mortality.[27]

Do the CAST results apply to other populations as well? The overall mortality effect of encainide and flecainide was about the same early and late after infarction so that their adverse effect is not restricted to the healing period after myocardial infarction. However, previous infarction may be necessary for the adverse effect of encainide and flecainide to express itself. If so, the findings in the CAST do not necessarily apply to other groups of patients with heart disease. The European view is that the CAST results should not be extrapolated beyond the population actually studied in the CAST.[28] The American view is that the closer a patient is to those studied in the CAST, the greater the concern when considering the use of class I antiarrhythmic drugs. The risk/benefit ratio should be considered carefully in patients with structural heart disease and ventricular arrhythmias. Most physicians in the United States and in Europe believe that patients with supraventricular arrhythmias who do not have structural heart disease are sufficiently different from those in the CAST to have a lower level of concern even though encainide and flecainide have not been proved safe in these patients. On October 6, the Cardiovascular and Renal Drugs Advisory Board to the FDA recommended approval of flecainide for this use.

Has the problem of sudden cardiac death after myocardial infarction gone away? The most recent data available indicate that changes in conventional treatment have not changed the significance of ventricular arrhythmias after myocardial infarction.[29] Ventricular arrhythmias still double the risk of dying within 2 years of myocardial infarction after adjusting for left ventricular dysfunction and other variables.[30-34] It would be reasonable to expect widespread efforts to achieve reperfusion of ischemic myocardium early in the course of myocardial infarction to decrease the prevalence of left ventricular dysfunction and ventricular arrhythmias. However, it is unlikely that these measures will alter the relation between left ventricular dysfunction and ventricular arrhythmias with increased mortality rates.

What will be the public health impact of the CAST? Recent surveys suggest that about half of the patients like those recruited for the CAST were treated with antiarrhythmic drugs with class I action.[35,36] Until the preliminary CAST results were available, the fastest growing segment of the antiarrhythmic drug market was the drugs with class IC action. When the results of the CAST have been adequately communicated to practitioners, a marked reduction in the use of drugs with class I antiarrhythmic action should be seen in patients with postinfarction ventricular arrhythmias and a corresponding increase in the use of β blockers. If this prediction is correct, we can expect the changes in medical practice as a result of the CAST to save several thousand lives per year. The CAST results will stimulate a thorough reexamination of the safety standards for all drugs. We are likely to see guidelines for drug development that give more emphasis to the assessment of mortality as an end point. If so, the cost of drug development will go up and new models for safety assessment and new cost-sharing arrangements are likely to emerge. In the future, we will demand stronger safety standards for drugs and we will have to find new ways to conduct or to fund safety assessment in order to make more stringent safety assessment feasible.

Why was the mortality rate so low in the placebo group in the main trial? The possible reasons for the low mortality rate were given in the CAST article appearing in the *The New England Journal of Medicine* on August 10, 1989. New conventional treatments, e.g., thrombolysis and angioplasty, might lower the mortality rate substantially. This factor should affect the number of eligible patients more than the mortality rate of those who are eligible. The sickest patients were not enrolled. This is probably not the case (read later). The follow-up was short, i.e., an average of 10 months. Nonsudden deaths predominate early, sudden deaths occur proportionately more frequently later.[32] This accounts for some, but certainly not all, of the low mortality in the placebo group. A positive response to an antiarrhythmic drug selects low-risk patients. In considering all patients who signed a CAST consent form, the 1-year total mortality rate was about 8% which is only slightly less than the anticipated rate. This figure subtracts the deaths attributable to drug. This is a minimum figure because the mortality status has not been determined for about 40% of the group that was not randomized either to the main study or to the substudy for patients whose arrhythmia was partially suppressed. These figures suggest that the main reason for the low mortality rate in the placebo group in the main trial is that patients who started titration but were not randomized had a much higher mortality than those who tolerated the drugs well, were suppressed, and were randomized. Patients whose ventricular arrhythmias were suppressed during open-label titration had a lower mortality rate than those whose ventricular arrhythmias were not suppressed even though treatment was withdrawn after titration. Thus, suppression of ventricular arrhyth-

mias may be identifying a patient characteristic as much as identifying an effective drug.[37] The CAST protocol mimics clinical practice closely, and everybody who could be treated was treated. During titration, the sickest people died, did not have suppression or had increases in arrhythmia, or had pulmonary edema or some other adverse effect that prompted their doctor to discontinue treatment. These same events would cause treatment to be discontinued in conventional clinical practice.

Why wasn't the CAST stopped altogether; what is happening now? First, the Data, Safety and Monitoring Board, the only group who has seen the moricizne data, recommended in the strongest terms that moricizine should be continued in the CAST even though encainide and flecainide should be removed. Evidently, there were striking differences between moricizine and the other drugs. Moricizine is worthy of further testing and it seems unlikely that moricizine will be harmful. But consider the difference in the future of clinical practice and of drug development by industry with 2 different possible outcomes. If results show that when moricizine suppresses arrhythmias it improves survival, it will be used to treat asymptomatic ventricular arrhythmias after myocardial infarction. The market for antiarrhythmic drugs will expand substantially. Such a finding also will encourage the drug industry to search for other chemical entities with class I antiarrhythmic action that not only improve survival but also have other advantages, e.g., once-a-day dosing and less noncardiac adverse effects. If results show that when moricizine suppresses arrhythmias it has no effect on survival, the drug will be used only to treat symptomatic ventricular arrhythmias, a much smaller market. However, moricizine can be used with confidence that no harm is being caused while controlling symptoms. This outcome will provide much less incentive for the American drug industry to develop new drugs to treat ventricular arrhythmias. The importance of substantial suppression vs mere treatment of the arrhythmia can be assessed by comparing the active treatment groups in the main study and in the substudy for patients who have partial suppression. Also, comparing the placebo groups in the main study with the substudy for patients with partial suppression will establish the prognostic significance of suppression during titration. With the information available, it seems that patients whose arrhythmias can be suppressed during titration with antiarrhythmic drugs have a better survival experience than patients whose arrhythmias are not suppressed even when drug treatment is discontinued after titration. These findings indicate that suppressibility is an important prognostic indicator.

There are many important questions left that can be answered by the CAST. The protocol has been changed: encainide and flecainide were removed, the qualifying ejection fraction was reduced to 40%, the enrolling window was shortened to 6 to 90 days, and a third dose of moricizine, 900 mg/day, was added. These measures should lead to a higher risk group being enrolled and safer treatment. The CAST is enrolling actively and asks physicians for support by encouraging their patients with postinfarction ventricular arrhythmias to participate.

REFERENCES

1. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Increased mortality due to encainide or flecainide in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med 1989;321:406–412.*

2. Ruskin JN. The Cardiac Arrhythmia Suppression Trial (CAST). *N Engl J Med 1989;321:386–387.*

3. Pratt CM, Brater CD, Harrell FE Jr, Kowey PR, Leier CV, Lowenthal DT, Messerli FH, Packer M, Pritchett ELC, Ruskin JN. Clinical and regulatory implications of the Cardiac Arrhythmia Suppression Trial (CAST). *Am J Cardiol 1990; in press.*

4. Velebit V, Podrid P, Lown B, Cohen BH, Graboys TB. Aggravation and provocation of ventricular arrhythmias by arrhythmic drugs. *Circulation 1982; 65:886–894.*

5. Bigger JT Jr, Sahar DI. Clinical types of proarrhythmic response to antiarrhythmic drugs. *Am J Cardiol 1987;59:2E–9E.*

6. Minardo JD, Heger JJ, Miles WM, Zipes DP, Prystowsky EN. Clinical characteristics of patients with ventricular fibrillation during antiarrhythmic drug therapy. *N Engl J Med 1988;319:257–262.*

7. Stanton MS, Prystowsky EN, Fineberg NS, Miles WM, Zipes DP, Heger JJ. Arrhythmogenic effects of antiarrhythmic drugs: a study of 506 patients treated for ventricular tachycardia or fibrillation. *JACC 1989;14:209–215.*

8. Morganroth J, Borland M, Chao G. Application of a frequency definition of ventricular proarrhythmia. *Am J Cardiol 1987;59:97–99.*

9. Zimmerman JM, Bigger JT, Coromilas J. Flecainide acetate is arrhythmogenic in a canine model of sustained ventricular tachycardia (abstr). *JACC 1985;5:391.*

10. Kou WH, Nelson SD, Lynch JJ, Montgomery DG, DiCarlo L, Lucchesi BR. Effect of flecainide acetate on prevention of electrical induction of ventricular tachycardia and occurrence of ischemic ventricular fibrillation during the early postmyocardial infarction period: evaluation in a conscious canine model of sudden death. *JACC 1987;9:359–365.*

11. Coromilas J, Saltman AE, Waldecker B, Dillon SM, Wit AL. Effect of class IC antiarrhythmic drugs on anisotropic reentry in canine infarcts (abstr). *Circulation 1988;78:II:II-460.*

12. Lynch JJ, DiCarlo LA, Montgomery DG, Lucchesi BR. Effects of flecainide acetate on ventricular tachyarrhythmia and fibrillation in dogs with recent myocardial infarction. *Pharmacology 1987;35:181–193.*

13. de Paola AAV, Horowitz LN, Morganroth J, Senior S, Spielman SR, Greenspan AM, Kay HR. Influence of left ventricular dysfunction on flecainide therapy. *JACC 1987;9:163–168.*

14. Slater W, Lampert S, Podrid PJ, Lown B. Clinical predictors of arrhythmia worsening by antiarrhythmic drugs. *Am J Cardiol 1988;61:349–353.*

15. Tordjman T, Podrid PJ, Raeder E, Lown B. Safety and efficacy of encainide for malignant ventricular arrhythmias. *Am J Cardiol 1986;58:87C–95C.*

16. Patterson E, Lucchesi BR. Antifibrillatory actions of nadolol. *J Pharmacol Exp Ther 1982;223:144–152.*

17. Patterson E, Lynch JJ, Lucchesi BR. Antiarrhythmic and antifibrillatory actions of the beta-adrenergic receptor antagonist, dl-sotalol. *J Pharmacol Exp Ther 1984;230:519–526.*

18. Patterson E, Eller BT, Abrams GD, Vasiliades J, Lucchesi BR. Ventricular fibrillation in a conscious canine preparation of sudden coronary death: prevention by short- and long-term amiodarone administration. *Circulation 1983;68:857–864.*

19. Falk RH. Flecainide-induced ventricular tachycardia and fibrillation in patients treated for atrial fibrillation. *Ann Intern Med 1989;111:107–111.*

20. Anastasiou-Nana MI, Anderson JL, Stewart JR, Crevey BJ, Yanowitz FG, Lutz JR, Johnson TA. Occurrence of exercise-induced and spontaneous wide complex tachycardia during therapy with flecainide for complex ventricular arrhythmias: a probable proarrhythmic effect. *Am Heart J 1987;113:1071–1077.*

21. May GS, Eberlein KA, Furberg CD, Passamani ER, DeMets DL. Secondary prevention after myocardial infarction: a review of long-term trials. *Prog Cardiovasc Dis 1982;24:331–352.*

22. Furberg CD. Effect of antiarrhythmic drugs on mortality after myocardial infarction. *Am J Cardiol 1983;52:32C–36C.*

23. Hine L, Laird N, Hewitt P, Chalmers T. Meta-analysis of empiric chronic antiarrhythmic therapy after myocardial infarction. *JAMA 1989;262:3037–3040.*

24. Coplen SE, Antman EM, Berlin JA, Hewitt P, Chalmers TC. Prevention of recurrent atrial fibrillation by quinidine. A meta-analysis of randomized trials (abstr). *Circulation 1989;80:II:II-633.*

25. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis 1985;27:335–371.*

26. Bigger JT Jr, Coromilas J, Rolnitzky LM, Fleiss JL, Kleiger RE, and The Multicenter Diltiazem Post-Infarction Trial Investigators. Effect of diltiazem on cardiac rate and rhythm after myocardial infarction. *Am J Cardiol 1990;65:in press.*

27. Held PH, Yusuf S, Furberg CD. Calcium channel blockers in acute myocardial infarction and unstable angina: an overview of the result from the randomized trials. *Br Med J 1989; in press.*

28. Editorial. Flecainide and CAST. *Lancet 1989;2:481–482.*

29. Coromilas J, Bigger JT Jr, Kleiger RE, Rolnitzky LM, Fleiss JL, and the MDPIT Research Group. Relations among left ventricular dysfunction, ventricular arrhythmias, and mortality after myocardial infarction. *Circulation 1989; 80:suppl II:II-48.*

30. Ruberman W, Weinblatt E, Goldberg JD, Frank CW, Shapiro S. Ventricular premature beats and mortality after myocardial infarction. *N Engl J Med 1977;297:750–757.*

31. Moss AJ, Davis HT, DeCamilla J, Bayer LW. Ventricular ectopic beats and their relation to sudden and nonsudden cardiac death after myocardial infarction. *Circulation 1979;60:998–1003.*

32. Bigger JT Jr, Fleiss JL, Kleiger R, Miller JP, Rolnitzky LM and the Multicenter Post-Infarction Research Group. The relationship among ventricular arrhythmias, left ventricular dysfunction and mortality in the 2 years after myocardial infarction. *Circulation 1984;69:250–258.*

33. Mukherji J, Rude RE, Poole KE, Gustafson N, Thomas LJ Jr, Strauss HW, Jaffe AS, Muller JE, Roberts R, Raabe DS Jr, Croft CH, Passamani E, Braunwald E, Willerson JT, and the MILIS Study Group. Risk factors for sudden death after acute myocardial infarction: two-year follow-up. *Am J Cardiol 1984;54:31–36.*

34. Nicod P, Gilpin E, Dittrich H, Henning H, Ross J Jr. Prognostic significance of complex ventricular arrhythmia for cardiac death during the first year after myocardial infarction. *J Electrophysiol 1987;1:93–102.*

35. Vlay S. How the university cardiologist treats ventricular premature beats: a nationwide survey of 65 university medical centers. *Am Heart J 1985;110:904–909.*

36. Morganroth J, Bigger JT, Anderson JL. Treatment of ventricular arrhythmias by United States cardiologists: a survey before the Cardiac Arrhythmia Suppression Trial (CAST) results were available. *Am J Cardiol 1990;65:40–48.*

37. Graboys TB, Lown B, Podrid PJ, DeSilva R. Long term survival of patients with ventricular arrhythmia treated with antiarrhythmic drugs. *Am J Cardiol 1982;50:437–443.*

Clinical Development of Moricizine as an Antiarrhythmic Agent

Sara Armstrong Mahler, MD, and R. Michael Borland, MD, PhD

The primary development of moricizine as an antiarrhythmic agent has occurred in the Soviet Union and the United States. The data in this presentation are based on the 1,844 subjects/patients (1,817 adults and 27 pediatric patients) who participated in 34 controlled studies and 3 uncontrolled compassionate-use programs conducted in the United States. Of the 1,817 adults, 443 received only placebo or comparative agents and 1,374 received moricizine in daily doses of 50 to 1,800 mg.

A total of 1,190 adult patients (mean age 59 years) had ventricular arrhythmias classified as either benign (8%), potentially lethal (58%) or lethal (33%). Most patients had a history of ≥1 cardiovascular disease, including coronary artery disease, previous myocardial infarction and congestive heart failure.

Antiarrhythmic activity was assessed by four methods: 24-hour ambulatory electrocardiographic monitoring, programmed electrical stimulation, exercise tolerance tests, and global evaluation (only for some patients in the compassionate-use program). In addition, the effects of moricizine on symptoms associated with ventricular arrhythmias were assessed.

The safety variables evaluated included adverse experiences, proarrhythmia, congestive heart failure, other cardiovascular effects, death, chest x-ray, ophthalmic examinations, neuroleptic phenothiazine effects and clinical laboratory tests.

(Am J Cardiol 1990;65:11D–14D)

From Medical Research, Medical Products Department, E. I. Du Pont de Nemours & Company, Inc., Wilmington, Delaware.

Address for reprints: Sara Armstrong Mahler, MD, E. I. Du Pont de Nemours & Company, Inc., Medical Products Department, P.O. Box 80026, Wilmington, Delaware 19880-0026.

The development of moricizine as an antiarrhythmic agent has occurred mainly in 2 countries, the Soviet Union and the United States, during a 25-year period. Moricizine was synthesized in 1964 and initially evaluated (preclinically and clinically) in the Soviet Union where oral, intravenous and intramuscular formulations have been in general use since 1971.[1,2] Du Pont Pharmaceuticals licensed moricizine from the Soviet Union and initiated additional preclinical studies in 1974. In 1976, the clinical program with the oral formulation began in the United States. The clinical development was interrupted on 2 occasions because of preclinical findings. The first occurred in 1978 when there were unexplained monkey deaths which were later determined to be the result of a dosing procedure error. The second was in 1982, due to the presence of proliferative rat liver changes which were subsequently classified as hyperplastic nodules. The clinical data developed in the United States (plus 1 Canadian site) and submitted in the New Drug Application in 1987 are reviewed in this report.

METHODS

Clinical program: The clinical studies conducted in the Soviet Union, Western Europe and the United States include a total of more than 2,942 persons of whom 2,499 received moricizine. There are 39 published clinical trials in which the oral, intravenous or intramuscular moricizine formulations, or any combination of these, were evaluated in more than 1,000 children or adults in the Soviet Union, and 10 Western European studies in which 98 adults with ventricular arrhythmias received the oral formulation. However, the data in this presentation are primarily based on the 1,844 subjects/patients who participated in 37 studies conducted in the United States and at 1 site located in Canada.

The United States clinical program conducted from June 1976 through February 1987 consists of 34 controlled studies and 3 uncontrolled compassionate-use programs. The controlled studies include 17 designed primarily to assess clinical pharmacology and 17 in which the main objective was to define the activity of moricizine in patients with ventricular arrhythmias. In the latter studies, information was obtained about the activity of daily oral doses of moricizine ranging from 150 to 1,800 mg; the onset, offset and duration of activity; activity of moricizine vs placebo and other active controls (disopyramide, encainide, flecainide, imipramine, propranolol and quinidine); and the short- and long-term activity in patients with benign, potentially lethal and lethal ventricu-

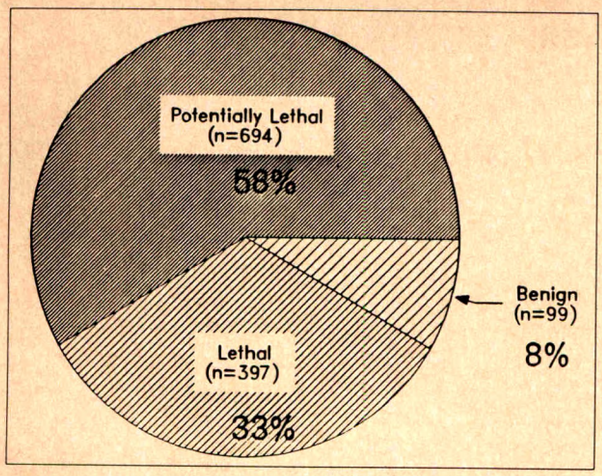


FIGURE 1. Ventricular arrhythmia classification for 1,190 patients treated with moricizine for ventricular ectopic activity.

lar arrhythmias.[3–11] In many of these studies there were important secondary objectives. For example, in 1 long-term dosing study, a subgroup of patients with ventricular tachycardia (VT) and left ventricular dysfunction were evaluated at rest and during exercise to assess moricizine's hemodynamic effects.[12] Sixteen of the controlled activity studies were sponsored by Du Pont Pharmaceuticals and 1 (the Cardiac Arrhythmia Pilot Study) was sponsored by the National Heart, Lung, and Blood Institute. The purpose of the compassionate-use programs was to treat patients (adults and children) who had supraventricular or ventricular (most of which were life-threatening) arrhythmias and in whom all marketed antiarrhythmic drugs were either ineffective, not tolerated or contraindicated, or any combination of these.

The safety of moricizine was evaluated in all controlled studies and the compassionate-use programs.

Data obtained on 121 subjects/patients who participated in 8 additional clinical pharmacology studies conducted in the United States since the New Drug Application submission are also discussed. The objectives of these studies were to assess the effects of moricizine on the pharmacokinetics or pharmacodynamics, or both, of concomitantly administered captopril, diltiazem, theophylline and warfarin; to compare the pharmacokinetics of moricizine in healthy subjects with that in patients with renal and hepatic impairment; and to determine the effects of moricizine on antipyrine clearance.

Study population: During an 11-year period, a total of 1,844 persons (1,817 adults and 27 pediatric patients) participated in studies conducted in the United States. The 27 pediatric patients are excluded from this presentation. Therefore, the data being reviewed are for the 1,817 adults; 443 received only placebo or comparative agents and 1,374 received moricizine. The most frequently prescribed daily doses were 600, 750 and 900 mg, which were usually administered in 3 divided doses. There were 685 patient-years exposure and the duration of dosing ranged from 1 day to 7.2 years (mean 6 months), with 239 patients receiving the drug therapy for more than 1 year. Most patients were receiving concomitant cardiovascular medications, including diuretics (49%), vasodilators (47%), cardiac glycosides (40%), calcium channel blockers (19%) and β blockers (19%).

Of the 1,256 patients (age 18 to 86 years, 81% men) who received moricizine in the Du Pont–sponsored studies, 1,072 (85%) had ventricular arrhythmias, 33 (3%) had supraventricular arrhythmias and 151 (12%) did not have arrhythmias. All 118 patients (age 21 to 73 years, 85% men) in the Cardiac Arrhythmia Pilot Study had ventricular arrhythmias. Thus, 1,190 adult patients (age 18 to 86 years, mean 59) had ventricular arrhythmias. Each of these patients was classified as having either a benign, potentially lethal or lethal ventricular arrhythmia based on the patient's risk of sudden cardiac death. Most patients (495, 58%) had potentially lethal ventricular arrhythmias; 397 patients (33%) had lethal and 99 patients (8%) had benign ventricular arrhythmias (Fig. 1).

Of the 1,072 patients in the Du Pont–sponsored studies with ventricular arrhythmias, 518 (48%) had a history of symptoms associated with their arrhythmias. The remaining patients were either asymptomatic or had an unspecified history of arrhythmia symptoms. Most of this population (87%) had received from 1 to 15 antiarrhythmic drugs that were generally ineffective or not well-tolerated, or both. Most of them (93%) had a history of $\geq$1 cardiovascular disease other than arrhythmias, including coronary artery disease (67%), previous myocardial infarction (53%) and congestive heart failure (43%).

Methods of evaluation: Antiarrhythmic activity was assessed by 4 methods: 24-hour ambulatory electrocardiographic monitoring (Holter), programmed electrical stimulation, exercise tests, and global evaluation (only for some patients in the compassionate-use program). In addition, the effects of moricizine on symptoms associated with ventricular arrhythmias (palpitations, presyncope, syncope, cardiac arrest and seizures) were determined.

Holter monitoring was the principal method used in 72% of the patients in Du Pont–sponsored studies. Each patient underwent 2 to 54 (mean 13) Holter monitoring tests. A patient was required to have an average of $\geq$30 ventricular premature contractions (VPCs) per hour at baseline to be included in the analysis. Response was defined as $\geq$75% reduction in total VPCs. The geometric mean and median percent changes in frequency of VPCs per hour on the drug from baseline also were determined. Patients with nonsustained VT at baseline had to have abolition (in most studies) or $\geq$90% reduction of nonsustained VT runs to be classified as a responder.

In the programmed electrical stimulation studies, patients qualified if either sustained or nonsustained VT was induced at baseline. For the drug to be classifed as effective, there had to be abolition of the baseline-induced VT.

Criteria for efficacy during exercise tolerance testing with the drug compared with control included a 50% decrease in total VPCs per minute, $\geq$90% decrease in paired VPCs per minute and abolition of VT.

The safety evaluation of orally administered moricizine in the adults who participated in the Du Pont–spon-

sored clinical trials was primarily based on the following variables: (1) adverse experiences (both related and unrelated to the study drug by overall frequency, body system, duration of dosing, dosage, age, illness and concomitant therapy, and with attention to patients requiring a reduction in dosage or discontinuation of the study drug); (2) proarrhythmia; (3) congestive heart failure; (4) deaths; (5) cardiovascular effects (changes in the electrocardiogram, blood pressure, heart rate, left ventricular function and hemodynamics); (6) chest x-rays; (7) ophthalmic examinations; (8) typical neuroleptic phenothiazine evaluations (effects on serum prolactin levels and on movement, behavior and mood); and (9) clinical laboratory tests.

DISCUSSION

The development of moricizine as an antiarrhythmic agent has occurred over a 25-year period (1964 to 1989), initially in the Soviet Union and later mainly in the United States. Ethmozine, which has been spelled several ways (ethmozin, ethmosine, etmosin and ethmosin), was the first and only nonchemical name used to identify this compound for almost 20 years before it became a trademark (brand name) and moricizine was designated the generic name in the United States.

After many years of systematic search for a phenothiazine derivative with antiarrhythmic activity and a good safety profile, this compound was synthetized in 1964 at the Institute of Pharmacology of the USSR Academy of Medical Science in Moscow.[1] Preclinical experiments were conducted in many species in the Soviet Union.[2,13–18] The initial clinical development occurred in the Soviet Union during a 5-year period (1966 to 1971). The published and unpublished data included information on daily oral moricizine dosages of 30 to 225 mg administered for 5 to 30 days or parenteral daily doses of 50 to 200 mg which were evaluated in approximately 1,000 male and female adult (age 19 to 90 years) patients with supraventricular or ventricular arrhythmias.[19–24] Evaluation of drug efficacy was determined by short 1-lead electrocardiographic records or the patient's subjective evaluations, or both. Based on these results, the drug was approved in 1970 by the Pharmacological Committee of the USSR Minister of Health for widespread use in medical practice which began in 1971.[2] The recommended oral daily dosages of moricizine were 75 to 225 mg, given in 3 divided dosages, and the parenteral dosages were 50 to 100 mg per injection.

In 1974, the Du Pont Company licensed moricizine from Licensintorg of the Soviet Union. After conducting preclinical evaluations that included pharmacology, toxicology and metabolism studies in the United States, an Investigational New Drug application was filed and clinical trials were initiated in 1976.[25–28] The oral moricizine dosages used in the initial United States studies were those recommended in labeling in the Soviet Union (150 and 225 mg/day) and slightly higher (300 mg/day). These dosages were extremely well-tolerated but rarely efficacious; thus, the daily dosages were slowly and carefully increased (ranging from daily dosages of 450 to 900 mg) in hospitalized patients. The higher dosages were more efficacious and also were well tolerated.[29,30] The differences in the effective daily dosages in the United States vs those in early studies in the Soviet Union are probably due to the different methods of evaluation. The effectiveness of moricizine in suppressing supraventricular or ventricular arrhythmias, or both, in the first United States' studies was based on 24-hour ambulatory electrocardiograms (Holter monitoring) obtained daily for 13 consecutive days (controlled-placebo for 3 days, a specified fixed dose of moricizine for 7 days, following by placebo for 3 days), whereas the efficacy in the earlier USSR studies was determined by short electrocardiographic strips and the patient's subjective feelings before Holter techniques were available.

In 1977, Dr. Philip Podrid from the Harvard School of Public Health in Boston, Massachusetts, in collaboration with cardiologists in the Soviet Union, conducted a moricizine study in patients with ventricular arrhythmias at the National Cardiology Research Center in Moscow. The protocols, which included the use of Holters and exercise testing for acute and chronic antiarrhythmic activity were those developed and used in the Lown Cardiovascular Laboratories at the Harvard School of Public Health. Based on early clinical results in the United States, daily oral dosages larger than those previously administered in the Soviet Union were evaluated. Two daily dosages, 225 and 600 mg, were administered. Moricizine was efficacious in 2 of 11 patients (18%) who received 225 mg/day vs 14 of 26 patients (54%) who received 600 mg/day.[31] The moricizine daily dose was increased to 600 mg/day in the Soviet Union in 1978 as a result of these findings and again increased to 900 mg/day in 1985 based on additional clinical data from the Soviet Union and the United States.

Data from the United States studies also have contributed to basic knowledge about Holter evaluations of arrhythmias which include understanding the limitations of consecutive 24-hour Holters, the spontaneous variability of complex ventricular arrhythmias, the changing baseline of ventricular arrhythmias during long-term therapy and the natural history of benign and potentially malignant ventricular arrhythmias.[32–35]

REFERENCES

1. Gritsenko AN, Yermakova ZI, Zhuravlev SV. The synthesis of ethmozine—a new preparation with antiarrhythmic action. *Khimiko-Farmatsevticheskii Zhurnal 1971;6:17–19.*

2. Kaverina NV, Senova ZP, Vikhlyaev Yu I, Ul'yanova OV. On the antiarrhythmic properties of ethmozine. *Farmakologiya i Toksikologiya 1970;33:693–697.*

3. Morganroth J, Pratt CM, Kennedy HL, Singh SN, Platt ML, Baker BJ, Mason DT. Efficacy and tolerance of ethmozine (moricizine HCl) in placebo-controlled trials. *Am J Cardiol 1987;60:48F–51F.*

4. Pratt CM, Young JB, Francis ML, Taylor AA, Norton HJ, English L, Mann DE, Kopelen H, Quinones MA, Roberts R. Comparative effect of disopyramide and ethmozine in suppressing complex ventricular arrhythmias by use of a double-blind, placebo-controlled, longitudinal crossover design. *Circulation 1984;69:288–297.*

5. The Cardiac Arrhythmia Pilot Study (CAPS) Investigators: Effects of encainide, flecainide, imipramine and moricizine on ventricular arrhythmias during the year after acute myocardial infarction: the CAPS. *Am J Cardiol 1988;61:501–509.*

6. Butman SM, Knoll ML, Gardin JM. Comparison of ethmozine to propranolol and the combination for ventricular arrhythmias. *Am J Cardiol 1987;60:603–607.*

7. Kennedy HL, DeMaria AN, Sprague MK, Weene RD, Reed RM, Janosik DL, Buckingham TA. Comparative efficacy of moricizine and quinidine for benign and potentially lethal ventricular arrhythmia. *Am J Noninwas Cardiol 1988;2:98–105.*

8. Pratt CM, Yepsen SC, Taylor AA, Mason DT, Miller RR, Quinones MA, Lewis RA. Ethmozine suppression of single and repetitive ventricular premature depolarizations during therapy: documentation of efficacy and long-term safety. *Am Heart J 1983;106:85–91.*

9. Baker BJ, Murphy ML, Dinh H, Franciosa JA. Moricizine (ethmozine)—dose titration and long-term efficacy. *Clin Res 1984;32(5):A826.*

10. Gear K, Marcus FI, Huang SK, Fenster PE, Appleton C, Moeller V, Renaud G, Serokman R. Ethmozine for ventricular premature complexes. *Am J Cardiol 1986;57:946–949.*

11. Miura DS, Wynn J, Torres V, Laux B, Keefe D, Somberg J. Antiarrhythmic efficacy of ethmozine in patients with ventricular tachycardia as determined by programmed electrical stimulation. *Am Heart J 1986;111:661–666.*

12. Seals AA, English L, Leon CA, Wierman AM, Young JB, Zoghbi W, Quinones MA, Maher SA, Roberts R, Pratt CM. Hemodynamic effects of moricizine at rest and during supine bicycle exercise: results in patients with ventricular tachycardia and left ventricular dysfunction. *Am Heart J 1986;112(1):36–43.*

13. Kaverina NV, Senova ZP, Mitrofanov V, Rumova MF. On the pharmacology of etmosin—a new antiarrhythmic drug. *Farmakologiya i Toksikologiya 1972;35:182–185.*

14. Senova ZP, Lvov MV. On the mode of antiarrhythmic action of aetmozine. *Farmakologiya i Toksikologiya 1973;36:703–706.*

15. Boiko SS, Lyubimov BI. Distribution of aethmozine in the organism of white rats following single and repeated administration. *Farmakologiya i Toksikologiya 1974;37:152–155.*

16. Nanaeva MT. Effect of some antiarrhythmic drugs on animals with experimental arrhythmias under low-altitude and high-altitude conditions. *Trudy Kirgizskogo Gosudarstvennog Meditsinskogo Instituta 1975;103:113–118.*

17. Lyubimov BI, Mitrofanov VS, Porfir'eva RP. Chronic toxicity of ethmozine—a new antiarrhythmic agent. *Khimiko-Farmatsevticheskii Zhurnal 1976;10:147–149.*

18. Lyubimov BI, Mitrofanov VS, Porfir'eva RP, Smolnikova NM, Strekalova SN, Sharov PA. On the toxicity of aethmozine—a new antiarrhythmic agent (6-month experience of application). *Farmakologiya i Toksikologiya 1976;39:159–163.*

19. Ostapyuk FE. The effect of ethmozine on cardiac arrhythmias in patients with coronary insufficiency, myocardial infarction and cardiosclerosis. *Terapevticheskii Arkhiv 1969;41:73–77.*

20. Zaslavskaya RM, Skorobogatova IF, Kulbanovskaya EYa. Ethmosine medication of patients with deranged rhythm of the cardiac activity. *Sovetskaya Meditsina 1969;32:59–62.*

21. Gomzyakova TG. Results of clinical studies of the antiarrhythmic drug carbazin (ethmozin). *Vrachebnoe Delo 1970;4:62–64.*

22. Votchal BE, Lozinskii LG. Effectiveness of the new antiarrhythmic compound ethmozine. *Klinicheskaya Meditsina 1971;10:16–21.*

23. Senova ZP. Antiarrhythmic properties of phenothiazine derivatives. Successes in creating new medicinal substances. *Kharkevich, Moscow, 1974:288–300.*

24. Zakusov VV. Principles of studies of pharmacological substances. *Vestnik Akademii Meditsinskikh Nauk USSR 1976;9:7–14.*

25. Danilo P, Langan WB, Rosen MR, Hoffman BF. Effects of the phenothiazine analog, EN-313, on ventricular arrhythmias in the dog. *Eur J Pharmacol 1977;45:127–139.*

26. Boyden PB, Hoffman BF. A canine model of supraventricular arrhythmia (abstr). *Fed Proc 1978;37:817.*

27. Dangman KH, Hoffman BF. The effects of EN-313 on abnormal automaticity in canine cardiac Purkinje fibers (abstr). *Circulation 1978;56,58:suppl II:II-104.*

28. Ilvento J, Provet J, Rosen M. Accelerated idioventricular rhythm: a study of its mechanism in conscious dogs (abstr). *Circulation 1979;59,69:suppl II:II-86.*

29. Kennedy HL, Pescarmona JE, Joyner V, Caralis D, Poblete P. The efficacy and tolerance of ethmozin for chronic ventricular ectopy (abstr). *Circulation 1978;58:suppl II:II-177.*

30. Morganroth J, Pearlman AS, Dunkman WB, Horowitz LN, Josephson ME, Michelson EL. Ethmozin: a new antiarrhythmic agent developed in the USSR. Efficacy and tolerance. *Am Heart J 1979;98:621–628.*

31. Podrid PJ, Lyakishev A, Lown B, Mazur N. Ethmozin—a new antiarrhythmic drug for suppressing ventricular premature complexes. *Circulation 1980;61:450–457.*

32. Morganroth J, Michelson EL, Horowitz LN, Josephson ME, Pearlman AS, Duckman WB. Limitations of routine long-term electrocardiographic monitoring to assess ventricular ectopic frequency. *Circulation 1978;58:408–414.*

33. Michelson EL, Morganroth J. Spontaneous variability of complex ventricular arrhythmias detected by long-term electrocardiographic recording. *Circulation 1980;61:690–695.*

34. Pratt CM, Delclos G, Wierman AM, Mahler SA, Seals AA, Leon CA, Young JB, Quinones MA, Roberts R. The changing baseline of complex ventricular arrhythmias: a new consideration in assessing long-term antiarrhythmic drug therapy. *N Engl J Med 1985;313(23):1444–1449.*

35. Pratt CM, Francis M, Mahler SA, Aogaichi K, Keus, Young JB. The natural history of benign and potentially malignant ventricular arrhythmias with special reference to nonsustained ventricular tachycardia. *Am Heart J 1988;116:897–903.*

Cardiac Electrophysiologic Effects of Moricizine Hydrochloride

J. Thomas Bigger, Jr., MD

Moricizine is a class I antiarrhythmic drug. In preclinical studies, it produces a concentration-dependent decrease in the maximal rate of phase 0 depolarization, speeds repolarization of phases 2 and 3, and decreases the action potential duration and effective refractory period duration in cardiac Purkinje fibers. It has no effect on the slope of phase 4 depolarization, but suppresses normal automaticity in vitro and in vivo and suppresses abnormal automaticity in depolarized Purkinje fibers. Also, it suppresses early afterdepolarizations, delayed afterdepolarizations and triggered activity.

In patients, moricizine has minimal effects on the normal sinus node, slows conduction in the atrium, atrioventricular node, His-Purkinje system and ventricular myocardium and has little effect on the atrial and ventricular refractoriness.

The intensity of moricizine action on the atrioventricular node, His-Purkinje system and JT interval are dose-related. Co-administration of digoxin and moricizine intensified the lengthening of the PR, AH and HV intervals, and produced more shortening of the JT interval. Patients in whom moricizine was efficacious had a significantly greater lengthening of the AH and QRS intervals than those in whom moricizine was not efficacious. In some patients with sinus node dysfunction, moricizine produced sinus bradycardia, increased sinus node recovery time, and produced second-degree or complete sinoatrial block.

(Am J Cardiol 1990;65:15D-20D)

From the Division of Cardiology, Department of Medicine, Columbia University, New York, New York.

Address for reprints: J. Thomas Bigger, Jr., MD, Arrhythmia Control Unit, Columbia-Presbyterian Medical Center, 630 West 168th Street, New York, New York 10032.

The purpose of this review is to highlight basic and clinical electrophysiologic features of moricizine that importantly determine its efficacy or adverse effects when used to treat ventricular arrhythmias.

Electrophysiology: *Preclinical:* The effect of moricizine was studied on the transmembrane potential of isolated canine Purkinje fibers perfused with either blood from a donor dog administered the drug or Tyrode solution containing the drug.[1-3] Moricizine produced a concentration-dependent decrease in the maximal rate of depolarization during phase 0 (Vmax) and only high concentrations produced a slight decrease in conduction velocity. The membrane responsiveness curve was shifted to a more negative position on the voltage axis. Similarly, the h infinity curve shifted in a negative direction during superfusion with 1 μg/ml moricizine.[3] Voltage clamp studies in isolated canine cardiac Purkinje cells showed that 2 μM moricizine has significant "tonic" block of sodium ion (Na^+) current (I_{Na}), i.e., in noninactivated cells held at a transmembrane voltage of -150 mV.[4] Cells were activated at frequencies from 0.625 to 4 Hz to study use-dependent block of I_{Na}. The block of I_{Na} increased substantially with increasing frequency of activation. The intensity of use-dependent block of I_{Na} also was concentration dependent. The range of concentrations studied was 2 to 20 μM. These findings suggest that moricizine reaches its channel binding site when the channel is in its open state and unbinds independent of the kinetic state of the channel. Moricizine produced marked delay in conduction in the ischemic zone during acute coronary occlusion.[5]

Moricizine decreases excitability of cardiac Purkinje fibers by increasing the amplitude of intracellular current injection needed to depolarize fibers to threshold voltage, by blocking the Na^+ channel, by decreasing membrane resistance, and by moving threshold voltage to less negative values.[6] Many of these effects resemble those of lidocaine more than those of quinidine and procainamide. Moricizine increased the speed of repolarization of both phases 2 and 3, causing a decrease in the action potential duration and effective refractory period. The effects on repolarization are similar in many respects to lidocaine. When short segments of canine and ovine Purkinje fibers were exposed to calcium ion (Ca^{2+}) channel agonist Bay K 8644, the plateau of the action potential lengthened and early afterdepolarizations often occurred with an average take-off potential of -34 mV.[7,8] Several factors were shown to promote early afterdepolarizations: low frequency of stimulation, low $[K]_o$, application of tetra-

TABLE I Electrophysiologic Properties of Moricizine in Canine Cardiac Purkinje Fibers

Produces concentration-dependent decrease in maximal rate of depolarization during phase 0
Speeds repolarization of phase 2 and 3; suppresses early after depolarizations
Decreases the duration of the action potential duration and effective refractory period (canine Purkinje fibers)
Only high concentrations (fivefold human dose of 12 mg/kg/day) decrease action potential amplitude and maximal diastolic potential
No effect on slope of phase 4 depolarization, but suppresses normal and abnormal automaticity
Suppresses delayed afterdepolarizations in subacute myocardial infarction and digitalis toxicity

ethyl ammonium (to increase membrane resistance), or application of depolarizing current during the plateau of the action potential. During application of Bay K 8644, moricizine was capable of shortening action potential plateau and suppressing early afterdepolarizations.[7,8] Because early afterdepolarizations are thought to be the electrophysiologic basis for torsades de pointes, the action of moricizine on plateau currents suggests that this drug would be unlikely to produce torsades de pointes as part of its toxic profile. Maximal diastolic potential and action potential amplitude were not significantly affected by low concentrations of moricizine, but high concentrations produced modest decreases in both.

Moricizine, even at high concentrations (fivefold higher than those produced in humans by a dose of 12 mg/kg), did not significantly change the slope of phase 4 depolarization in normal Purkinje fibers that were stimulated at regular intervals (Table I). Despite the lack of effect of moricizine on maximal diastolic transmembrane voltage or the slope of spontaneous phase 4 depolarization, it had a prominent suppressant effect on normal spontaneous automaticity in canine Purkinje fibers.[1,9] Also, it was effective at suppressing normal automaticity that had been augmented by superfusion with Tyrode solution with $[K]_o = 2.7$ mM or Tyrode solution containing epinephrine. This antiautomatic effect on normal Purkinje fibers was due entirely to a shift in the voltage threshold to less negative values.[1] Moricizine was more potent than lidocaine for suppressing normal automaticity. Moricizine also was quite effective for suppressing abnormal automaticity in Purkinje fibers depolarized by barium chloride or as a result of myocardial infarction. When moricizine was applied to fibers showing abnormal automaticity, the spontaneous activity usually stopped altogether. The results of these experiments caused Dangman and Hoffman[2] to speculate that moricizine counteracted abnormal automaticity by blocking an inward "window current" carried by Na^+. Moricizine also was capable of suppressing delayed afterdepolarizations and triggered activity seen in Purkinje fibers taken from the infarcted region of 24-hour old myocardial infarcts in dogs.[1] Also, moricizine suppressed delayed afterdepolarizations and triggered activity in canine Purkinje fibers caused by ouabain toxicity, but only in concentrations that depressed the amplitude and rate of rise of phase 0 of the action potential.[10] In the same series of experiments, procainamide and quinidine suppressed delayed afterdepolarizations without depressing the amplitude and rate of rise of phase 0 of the action potential.

These electrophysiologic effects of moricizine are likely to account for its antiarrhythmic effect on ventricular arrhythmias. The substantial effect on phase 0 depolarization (an effect on I_{Na}) could alter conduction in reentrant circuits. The effect of moricizine on repolarization in the plateau range of transmembrane voltage could terminate ventricular arrhythmias due to early afterdepolarizations. Moricizine also could suppress ventricular arrhythmias due to abnormal automaticity in depolarized fibers or those due to delayed afterdepolarizations and triggered activity. More studies are needed to establish the antiarrhythmic effect of moricizine in model arrhythmias in intact mammals.

Clinical effects of oral administration of moricizine (United States studies): The cardiac electrophysiologic effects of orally administered moricizine on the human conduction system were determined in the United States in 58 adult patients.[11] The patients were either undergoing diagnostic right-sided cardiac catheterization (6 patients) or having programmed electrical stimulation (52 patients). Most patients had severe coronary heart disease with left ventricular dysfunction and spontaneous sustained ventricular arrhythmias.

The control electrophysiologic study was performed after all antiarrhythmic drugs had been discontinued for at least 5 half-lives and were repeated after administration of either a single, oral dose of moricizine (6 patients) or after 2 to 59 days (mean of 7.1 ± 8.0) of moricizine dosing (52 patients). In the latter group, the electrophysiologic studies usually were performed within 8 hours of the previous moricizine dose.

Effects of single, oral moricizine doses: *Study population and dosing:* Five men and 1 woman aged 41 to 63 years (mean 55) were evaluated 0.5, 1, 1.5 and 2 hours after administration of a single, oral dose of moricizine. One patient had frequent ventricular and supraventricular ectopic activity, 1 patient had supraventricular tachycardia, and 4 patients had no arrhythmias or conduction disturbances. All patients had cardiovascular diseases.

The single moricizine doses ranged from 400 to 900 mg (mean 683). All patients were receiving concomitant medications. Two hours after the administration of the single oral dose of moricizine, only 2 variables were changed significantly. The atrial effective refractory period was shortened by an average of 13 ms (6%), (217 ms 2 hours after moricizine vs baseline value of 230 ms). The mean AH interval was slightly prolonged, 7 ms, during pacing at a 600-ms cycle length (the baseline mean value was 93 ms and the mean value with moricizine was 99 ms). The mean AH interval also was prolonged by 44 ms during sinus rhythm, but this change was not statistically significant. There was no change in HV interval during normal sinus rhythm or at a pacing cycle length of 600 ms.

A few variables showed trends that were not statistically significant. Sinus cycle length decreased by 36 and

16 ms at 1.5 and 2.0 hours, respectively. The corrected sinus node recovery time 2 hours after the dose increased by 47 and 16 ms at pacing cycle lengths of 500 and 600 ms, respectively. There were no clinically or statistically significant changes in the PR, QRS, QT, QTc and JT intervals that were measured before and between 3 and 5.5 hours and again between 18 and 22 hours after the single doses; however, most intervals were measured after the expected peak effect of the drug.

Effect of chronic administration (2 to 59 days) of moricizine: *Study population and dosing:* The effects of chronic moricizine dosing on the conduction system were determined for 52 adult patients (85% men and 15% women, aged 27 to 73 years [mean ± standard deviation 57 ± 10.6]) who were undergoing programmed electrical stimulation testing before moricizine (control) and during moricizine dosing.[11] Nine patients (17%) had potentially malignant and 43 patients (83%) had malignant ventricular arrhythmias. All patients had 1 or more cardiovascular illnesses, most often coronary heart disease (79%) with previous myocardial infarction (69%).

At baseline, 19% of the patients had abnormal (<120 or >200 ms) PR intervals, 56% had prolonged (>100 ms) QRS intervals, and 45% had prolonged (>430 ms) QTc intervals. No patients had abnormal baseline JT intervals (>360 ms). Four patients had pacemakers.

The moricizine daily dosage ranged from 600 to 1,500 mg (mean of 892 ± 192). Sixty percent of the patients received daily doses of 750 or 900 mg. The duration of dosing ranged from 2 to 59 days (mean 7.1 ± 8.0).

Overall effect of moricizine: Of the 24 electrophysiologic variables measured, there was a statistically significant change in only 8. The sinus cycle length and JT interval decreased, the duration of the PR, AH, HV, QRS and QTc intervals increased, and the right ventricular effective refractory period at a paced cycle length of 600 ms increased (Table II).

Moricizine had a minimal effect on sinus node function. Sinus cycle length decreased by 63 ms and sinus node recovery time decreased an average of 91 ms. Neither change was statistically significant. Moricizine had no significant effect on the corrected sinus node recovery time or the sinoatrial conduction time.

In this group of patients with ventricular arrhythmias, moricizine had no significant effect on intraatrial conduction time, but did delay impulse conduction in the atrioventricular (AV) node and His-Purkinje system. Moricizine caused significant lengthening of the PR, AH, HV and QRS intervals.

The duration of the JT interval decreased significantly. No significant change occurred in the duration of the QT interval. A slight, but statistically significant, lengthening of the QTc interval occurred, which reflects the increase in QRS duration.

Chazov et al[12] studied 16 patients with AV reciprocating tachycardia due to Wolff-Parkinson-White syndrome (n = 10) or with concealed bypass tract (n = 6). Nine of the 14 patients with inducible, sustained supraventricular tachycardia (64%) had termination with an intravenous injection of 1.5 to 2 mg/kg of moricizine (Table III). The drug also prevented induction of supraventricular tachycardia in 8 patients (57%) (4 with Wolff-Parkinson-White syndrome and 4 with concealed bypass tract). The cycle length of supraventricular tachycardia was increased about 10% by intravenous moricizine. The intravenous dose of moricizine that was effective against supraventricular tachycardia increased the PA interval by 48%, the AH and PR intervals by 15%, but had no significant effect on HV, QRS or QT intervals. The substantial effect of moricizine on the AV node also was documented in the perfused rabbit heart.[13]

TABLE II Effect of Moricizine on Clinical Electrophysiologic Variables

Variable	No. of Pts.	Control Values (ms)	Change with Moricizine ms	Change with Moricizine %
Sinus cycle length	37	807	−64	−8*
PR interval	43	177	+36	+20†
AH interval	39	87	+15	+17†
HV interval	45	56	+14	+26
QRS interval	47	114	+21	+19†
QTc interval	40	428	+20	+5
JT interval	43	265	−14	−5
RV ERP	22	246	+10	+4*

* $p < 0.05$; † $p < 0.01$.
RV = right ventricular; ERP = effective refractory period (CL 600 at RV apex).

Effects of moricizine with normal versus abnormal baseline values: The effects of moricizine on electrophysiologic variables based on normal vs abnormal baseline values were compared for 6 variables (sinus node recovery time, PR, HV, QRS, and QTc intervals; and the cycle length at which AV nodal Wenckebach occurred). These variables were selected because there were adequate numbers of abnormal baseline values in the 52 patients.

Moricizine produced only a statistically significant different change in normal compared with abnormal baseline values for 2 variables (the sinus node recovery time and the QTc interval). With moricizine, the sinus node recovery time was shortened by 14% (mean 153 ms) in patients with normal baseline values (n = 12, mean 1,085 ms), whereas it was prolonged by 5% (mean 58 ms) in those with increased baseline values (n = 5, mean 1,182 ms). Patients with normal QTc intervals (n = 22, mean 400 ms) at baseline had a 10% (mean 40 ms) increase in QTc with moricizine vs patients with long

TABLE III Effect of Intravenous Moricizine (1.5 to 2.0 mg/kg) on Electrophysiologic Intervals in Patients with Supraventricular Tachycardia due to Accessory Pathways

Terminated induced SVT	9/14 pts. (64%)
Prevented induction of SVT	8/14 pts. (57%)
Increase in SVT cycle length	10%
Increase in PA interval	48%
Increase in AH interval	15%
Increase in PR interval	15%

No change in HV, QRS or QT intervals.
SVT = supraventricular tachycardia.
Adapted from *Am Heart J.*[12]

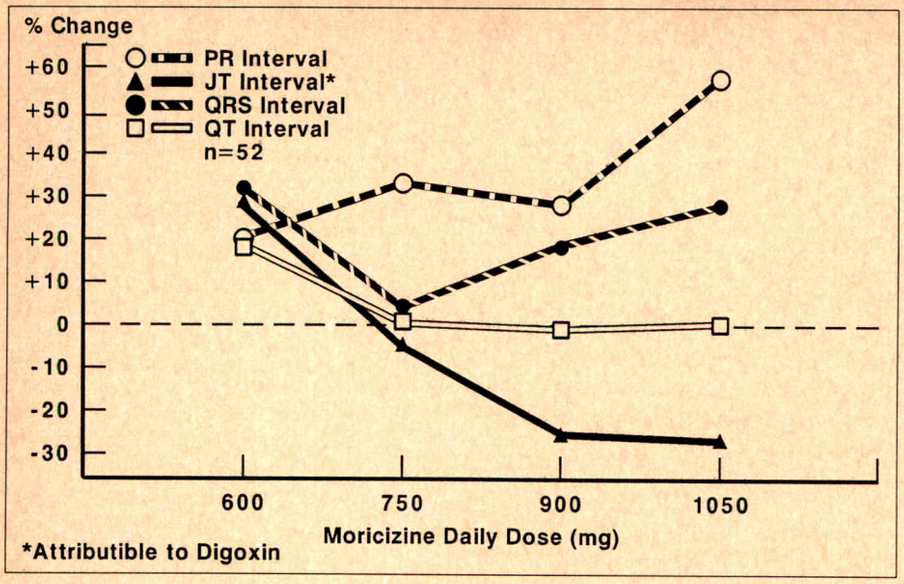


FIGURE 1. Changes in PR, QRS, QT and JT intervals as a function of moricizine dose in 52 patients undergoing electrophysiologic studies. Dose is plotted on the *X axis* and percent change on the *Y axis*. The *horizontal dashed line* indicates the baseline value (drug free).

QTc values (n = 18, mean 464 ms) at baseline who had a 1% (mean 3 ms) decrease in QTc with moricizine.

However, there was less lengthening of the PR and QRS intervals during moricizine dosing for those with prolonged baseline intervals than for those with normal baseline intervals. When the cycle length at which AV Wenckebach occurred was prolonged at baseline, it decreased with moricizine; when it was normal at baseline, it increased with moricizine.

Moricizine dose effect: A regression analysis of the change in the variable vs the moricizine dose was used to determine the effect of moricizine dose. The changes in the values of 4 variables (PR, AH, HV and JT intervals) were significantly dose related ($p < 0.05$). Larger moricizine doses produced more lengthening of the PR, AH and HV intervals, and more shortening of the JT interval. The QRS interval prolongation at the 900 and 1,050 mg/day doses was not statistically significant and the QT interval was not significantly changed by dose (Fig. 1).

Effect of co-administration of moricizine and digoxin: Thirty-one of the 52 patients (60%) received digoxin concomitantly with moricizine. The only variable that was significantly changed by the co-administration of moricizine and digoxin was the AH interval, which was more prolonged (by 13.1 ms) with the concomitant therapy (7.3 ms with moricizine alone vs 20.4 ms with moricizine and digoxin). The PR and HV intervals also prolonged more (14.4 and 7.1 ms, respectively) and the JT interval shortened more (17.5 ms) with the concomitant therapy, but these changes were not statistically significant.

Lengthening of the PR, AH and HV intervals and shortening of the JT interval tended to be greater when higher doses (≥900 mg/day) of moricizine were administered concomitantly with digoxin.

Relation of efficacy to electrophysiologic changes: Moricizine was evaluated in patients with ventricular arrhythmias either by 24-hour continuous electrocardiographic recordings (Holter) or by programmed electrical stimulation studies, or both. With Holter evaluation, efficacy was defined as ≥75% decrease in mean ventricular premature complexes per hour with moricizine compared with baseline or abolition of ventricular tachycardia, or both. Moricizine was efficacious in 33 patients (63%), not efficacious in 17 patients (33%), and efficacy was not evaluable in 2 patients (4%). The relation of efficacy of moricizine to changes in the conduction velocity (PR, AH, HV and QRS intervals) and ventricular repolarization (JT interval) was evaluated.

Patients in whom moricizine was efficacious had a statistically significantly greater prolongation of the AH and QRS intervals than those in whom moricizine was not efficacious. When the analysis of covariance was used to adjust for moricizine dose, the relation of the AH interval change to efficacy continued to be statistically significant ($p = 0.027$).

There was no statistically significant relation between changes in the PR, HV or JT intervals and efficacy. However, the PR and HV intervals were slightly more prolonged in patients who had efficacy; the JT interval shortened considerably less in the patients who responded to moricizine.

Effects of intravenous administration of moricizine (published USSR studies): *Study population and dosing:* Nine studies included data on the electrophysiologic effects of single, intravenously administered doses of moricizine (1.0 to 2.0 mg/kg; 150 mg) to 235 patients (age 13 to 77 years) with various types of cardiac arrhythmias that included sinus node dysfunction, Wolff-Parkinson-White syndrome, and supraventricular, atrioventricular nodal reentrant and ventricular tachycardias. Most of the 235 patients had supraventricular arrhythmias or sinus node dysfunction, or both; only 3 studies included patients with ventricular arrhythmias.

Electrophysiologic effects: In most studies, moricizine prolonged the PA interval (4 of 4 studies) and AH

interval (5 of 6 studies), indicating slowing of intraatrial and AV nodal conduction, respectively. Both the HV interval and sinoatrial conduction time increased slightly or were unaffected after injection of the drug. Conduction was delayed or blocked in accessory pathways (e.g., Kent bundle) in both the anterograde and retrograde directions, as well as in the ventriculoatrial conduction system. The effective refractory periods of the atrium, ventricle and AV node were not significantly changed by moricizine treatment in most of the studies in which these variables were measured (Table II).

Effects in patients with sinus node dysfunction: Like other class I antiarrhythmic drugs, moricizine may exacerbate impaired sinoatrial conduction. Rozenshtraukh[14] studied the electrophysiologic effects of moricizine (1.5 to 2.0 mg/kg intravenously) in 10 patients with sinus node dysfunction. Six of the patients responded similarly to those without sinus node dysfunction (i.e., sinus cycle length and sinus node recovery time decreased, while sinoatrial conduction time increased). However, the remaining 4 patients had significant increases in sinus cycle length, in sinus node recovery time, and in the corrected sinus node recovery time. Second-degree sinoatrial conduction block developed in 3 of the 4 patients, and in the remaining patient, who initially presented with second-degree block, sinoatrial block developed.

In a similar study by Rakovec et al,[15] 8 of 12 patients with prolonged sinus node recovery time (1,500 ms) at baseline had marked increases in sinus node recovery time and corrected sinus node time after 1 mg/kg of moricizine was administered intravenously.

In contrast to the reports by Rozenshtraukh and Rakovec, Sokolov et al[16] found only clinically insignificant changes in corrected sinus node dysfunction and sinoatrial conduction time in 3 patients with sinus node dysfunction who were given 150 mg of moricizine intravenously.

Electrophysiologic classification of moricizine: There is some confusion with the classification of moricizine by the Vaughan Williams system. Much of the confusion arises as a result of differences in concept about the key features used to classify the antiarrhythmic actions of drugs. Drugs with class I antiarrhythmic action bind to molecules in the Na^+ channel, impeding the inward surge of I_{Na} during activation. This molecular action translates into slowing of depolarization during phase 0 of the action potential and slowing of conduction, especially of premature impulses or those arising at low levels of transmembrane voltage. For many drugs, binding to the Na^+ channel is use-dependent, i.e., depends on the number of depolarizations per unit time. A hypothesis that explains this behavior is that the drug binds in the Na^+ channel only when it opens during activation. Drug unbinding may occur during any state of the channel, resting, open or inactivated. Most pharmacologists subclassify drugs by their intensity of action in blocking the Na^+ channel: IB weakest, IA intermediate potency and IC the strongest.[17] Actions on other channels are considered subsidiary. When Harrison[18] presented his modification of the Vaughan Williams classification, he featured effects on repolarization. He pointed out that drugs with class IA antiarrhythmic action tended to prolong action potential duration in ventricular tissues. Drugs with class IB antiarrhythmic action tended to shorten action potential duration. Drugs with class IC antiarrhythmic action had very little effect on repolarization. These effects are not uniform; e.g., procainamide has little effect on repolarization.

Clearly, when classified by intensity of effect on the Na^+ channel, moricizine has class IA antiarrhythmic action. However, unlike most drugs with class IA action, it shortens action potential duration in ventricular tissues. Also, moricizine depresses AV nodal conduction more than other drugs with class IA action, e.g., quinidine, procainamide or disopyramide.

Although the effect of moricizine on Na^+ channels undoubtedly contributes importantly to its antiarrhythmic action, it may or may not affect other ionic channels as well. More work needs to be done to characterize the molecular pharmacology of moricizine. Even the knowledge about moricizine's interaction with Na^+ channels is incomplete on a molecular level. For example, the rate constants for unbinding need additional clarification.

CONCLUSION

Moricizine is a class I antiarrhythmic drug. In preclinical studies, it produces a concentration-dependent decrease in maximal rate of phase 0 depolarization, speeds repolarization of phases 2 and 3, decreases action potential duration, and shortens effective refractory period duration in canine Purkinje fibers. It has no effect on the slope of phase 4 depolarization, but has a potent suppressant action on normal automaticity by increasing transmembrane threshold voltage. Also, moricizine suppresses abnormal automaticity in Purkinje fibers as a result of acute myocardial infarction or superfusion with barium chloride. In addition, it suppresses both early and delayed afterdepolarizations and triggered activity.

The clinical electrophysiologic properties of moricizine are summarized in Table II. In patients, moricizine delays the impulse conduction velocity in the atrium, atrioventricular node, His-Purkinje system and ventricular myocardium and has minimal effects on the normal sinus node and on the atrial and ventricular refractoriness. The action of moricizine on the PR, AH, HV and JT intervals is dose related. Concomitant administration of digoxin with moricizine, especially at higher doses, i.e., 900 mg, produced more lengthening of the PR, AH and HV intervals, and produced more shortening of the JT interval. Preliminary studies suggest that moricizine produces less increase of the PR, AH and HV intervals when baseline electrophysiologic measurements are abnormal than when they are normal. Conversely, moricizine was more likely to produce sinus bradycardia, increase sinus node recovery time, and produce second-degree or complete sinoatrial block in patients with sinus node dysfunction.

Also, preliminary data suggest that patients in whom moricizine was efficacious had a significantly greater prolongation of the AH and QRS intervals than those in whom moricizine was not efficacious.

The electrophysiology of moricizine is as complex as its chemistry and biotransformation. Although it best fits class IA of the Vaughan Williams classification based on its interactions with sarcolemmal Na^+ channels and conduction of the cardiac impulse, it has many other electrophysiologic effects that probably are important in its antiarrhythmic action. Thus, moricizine has a unique electrophysiologic profile and may as a result have a unique antiarrhythmic action.

REFERENCES

1. Danilo P Jr, Langan WB, Rosen MR, Hoffman BF. Effects of the phenothiazine derivative analog EN 313 on ventricular arrhythmias in dogs. *Eur J Pharmacol 1977;45:127–139.*

2. Dangman KH, Hoffman BF. Antiarrhythmic effects of ethmozin in cardiac Purkinje fibers: suppression of automaticity and abolition of triggering. *J Pharmacol Exp Ther 1983;227:578–586.*

3. Tsuji Y, Nishimura M, Osada M, Watanabe Y. Membrane action of ethmozin on normoxic and hypoxic canine Purkinje fibers. *J Cardiovasc Pharmacol 1983;5:961–967.*

4. Makielski JC, Undrovinas AI, Hanck DA, Sheets MF, Nesterenko VV, Alpert LA, Rosenshtraukh LV, Fozzard HA. Use-dependent block of sodium current by ethmozin in voltage-clamped internally perfused canine cardiac Purkinje cells. *J Mol Cell Cardiol 1988;20:255–265.*

5. Rosenshtraukh LV, Ruffy R, Elharrar V, Zipes D. Electrophysiologic effect of ethmozine on the dog's myocardium. *Kardiologiia 1979;19:63–72.*

6. Arnsdorf MF, Sawicki GJ. Effects of ethmozin on excitability in sheep Purkinje fibers: the balance among active and passive cellular properties which comprise the electrophysiologic matrix. *J Pharmacol Exp Ther 1989;248:1158–1166.*

7. January CT, Riddle JM, Salata JJ. A model for early afterdepolarizations: induction with the Ca^{2+} channel agonist Bay K 8644. *Circ Res 1988;62:563–571.*

8. Undrovinas AI, January C, Iuriavichus I, Riddle J, Zablotskaite D. Asymmetrical changes in electrical activity of Purkinje fibers and muscle cells after administration of BAY K 8644. A new model of cardiac arrhythmia. *Biull Vsesoiuznogo Kardiol Nauchn Tsentra AMN SSSR 1989;12(1):6–11.*

9. Dremin SA, Aniukhovskii EP, Rozenshtraukh LV, Hageman GR, Urtaler F. Action of ethacizin on normal and anomalous forms of Purkinje fiber automaticity in the dog. *Kardiologiia 1986;26:10–5.*

10. Hewett K, Gessman L, Rosen MR. Effects of procaine amide, quinidine and ethmozin on delayed afterdepolarizations. *Eur J Pharmacol 1983;96:21–28.*

11. Data on file in the Medical Products Department, E.I. du Pont de Nemours & Company, Inc., and in volume 125 of the New Drug Application, no. 19-753.

12. Chazov EI, Shugushev KK, Rosenshtraukh LV. Ethmozin. I. Effects of intravenous drug administration on paroxysmal supraventricular tachycardia in the ventricular preexcitation syndrome. *Am Heart J 1984;108:475–482.*

13. Dresel PE, Ogbaghebriel A, Abraham R. Electrophysiological effects of ethmozine in perfused rabbit hearts. *Can J Physiol Pharmacol 1985;63:1418–1422.*

14. Rozenshtraukh LV. Effect of ethmozine on the automatic function of the sinoatrial node and sinoatrial conduction in patients with normal and impaired function of the sinoatrial node. *Kardiologiia 1983;23:47–50.*

15. Rakovec P, Jakopin J, Rode P, Kenda MF, Horvat M. Electrophysiological effects of ethmozine on sinus nodal function in patients with and without sinus node dysfunction. *Eur Heart J 1984;5:243–246.*

16. Sokolov SF, Golitsyn SP, Mazur NA. Effect of ethmozine on the electrophysiological factors in patients with paroxysmal tachycardias: In: Theses of the All-Union Symposium on New Cardiovascular Medicinal Preparations (Erevan, USSR; September 19–21, 1979). *Printing House of the USSR Department of Health, Leningrad, 1979:80–82.*

17. Vaughan-Williams EM. A classification of antiarrhythmic actions reassessed after a decade of new drugs. *J Clin Pharmacol 1984;24:129–147.*

18. Harrison DC. Antiarrhythmic drug classification: New science and practical application. *Am J Cardiol 1985;56:185–187.*

Clinical Pharmacokinetics of Moricizine

Lyle A. Siddoway, MD, Sorell L. Schwartz, PhD, Jean T. Barbey, MD, and Raymond L. Woosley, MD, PhD

Moricizine is well absorbed after oral administration and undergoes extensive first-pass metabolism. The drug has a large apparent volume of distribution (approximately 4 liters/kg), exhibits extensive plasma protein binding (approximately 95%) and produces at least 30 metabolites. Indirect evidence indicates that some of those metabolites may be pharmacologically active. The elimination half-life of moricizine is 2 to 6 hours, but its duration of antiarrhythmic action is much longer suggesting active metabolites. Moricizine induces its own metabolism with no change in pharmacologic effect. It also induces the metabolism of theophylline and specific pathways of antipyrine. Cimetidine reduces metabolism of moricizine but does not alter its pharmacologic effects. This observation provides further support for the hypothesis that the metabolites of moricizine contribute to the pharmacologic actions during therapy and indicate that plasma level monitoring is not likely to be of value. There are no known clinically significant pharmacokinetic interactions between moricizine and digoxin, warfarin or propranolol. Excessive prolongation of the PR interval has been seen in some patients receiving both digoxin and moricizine, probably due to additive electrophysiologic effects of the 2 drugs.

(Am J Cardiol 1990;65:21D-25D)

From the Division of Clinical Pharmacology, Departments of Medicine and Pharmacology, Georgetown University of School of Medicine, Washington, D.C. Dr. Siddoway is a recipient of the Pharmaceutical Manufacturers Association Foundation Faculty Development Award in Clinical Pharmacology.

Address for reprints: Raymond L. Woosley, MD, PhD, Department of Pharmacology, Georgetown University Medical Center, 3900 Reservoir Road, N.W., Washington, DC 20007.

Moricizine is an antiarrhythmic agent developed in the Soviet Union and currently under review for licensing in the United States. Structurally, moricizine (Fig. 1) is composed of a phenothiazine nucleus and 2 side-chains. The morpholino side-chain appears to be necessary for its antiarrhythmic activity. Moricizine has a lower pK_a (6.4) than other phenothiazines, which may account in part for the lesser degree of central nervous system effect seen during its administration.

PHARMACOKINETICS

Woosley et al[1] reviewed the pharmacokinetics of moricizine, citing the relevant publications up to that time[2-4] and unpublished data provided by the manufacturer. That information is summarized here along with a presentation of further data provided by 2 manufacturer-sponsored studies.

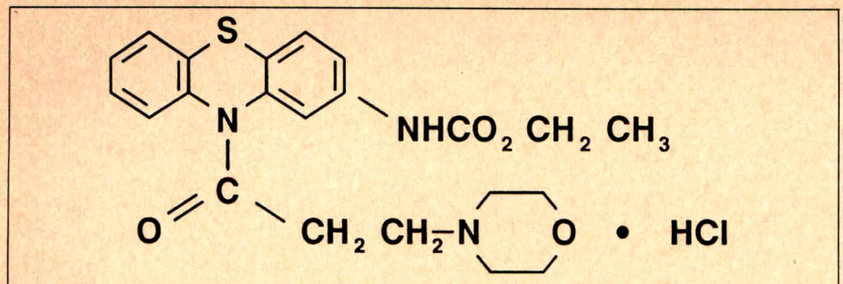
Intravenous administration of a single moricizine dose to normal subjects reveals classic 2-compartment pharmacokinetics. The half-time associated with the first exponent of the biexponential concentration-vs-time curve ("distribution half-life," $t_{1/2\alpha}$) is about 4 to 20 minutes. The half-time associated with the terminal slope ("terminal elimination half-life," $t_{1/2\beta}$) is about 2 to 6 hours.

After oral administration, peak blood levels are reached in 0.8 to 2.0 hours with a systemic bioavailability of 0.38, indicating a high hepatic intrinsic clearance (about 2.2 liters/min). Plasma protein binding is about 95%, with both albumin and α_1-acid glycoprotein as ligands. The volume of distribution estimated from the terminal phase of elimination (V_D) is about 300 liters. Considering the extent of plasma protein binding, this implies significant peripheral tissue binding.

Biotransformation of moricizine is virtually complete. After oral administration of radiolabeled moricizine, over half of the radioactivity was excreted in the urine, indicating significant enterohepatic cycling of the metabolites. The combined $t_{1/2}$ for the metabolites, as represented by radiolabel, is about 84 hours.

Further insight into moricizine clinical pharmacokinetics comes from a more recent multiple-dose study.* This study, involving 12 healthy male volunteers, used a 4-treatment, 4-period, sequential escalating multiple-dose protocol. The treatment groups were classified as 150, 200, 250 and 300 mg. The treatment periods were 1 dose every 8 hours for 7 days, with no washout period between treatments. Pharmacokinetic parameter values

*Du Pont study N-72, data on file, Du Pont Pharmaceuticals.



10-(3-Morpholinopropionyl) Phenothiazine-2-Carbamic Acid Ethyl Ester HCl

FIGURE 1. Structure of moricizine hydrochloride (HCl) (10-(3-morpholinopropionyl) phenothiazine-2-carbamic acid ethyl ester hydrochloride).

TABLE I Summary of Pharmacokinetic Findings of an Escalating Multiple Dose Study of Moricizine in 11 Subjects

Dosage	150 mg	200 mg	250 mg	300 mg
C_{min}* (mg/L)	0.016	0.017	0.019	0.018
	(0.008)	(0.011)	(0.011)	(0.010)
C_{max}* (mg/L)	0.607	0.666	0.600	0.597
	(0.308)	(0.281)	(0.264)	(0.296)
T_{max} (hr)	0.69	0.67	0.89	0.84
	(0.30)	(0.13)	(0.26)	(0.28)
AUC* (mg · hr/L)	1.138	1.220	1.21	0.993
	(0.464)	(0.561)	(0.488)	(0.423)
CL_o† (L/hr/kg)	4.03	3.85	3.77	3.89
	(1.77)	(1.59)	(1.52)	(1.68)
V_D (L/kg)	8.91	7.85	7.92	8.18
	(4.20)	(3.26)	(3.17)	(3.89)
$t_{1/2\beta}$	1.5	1.4	1.4	1.4
	(0.1)	(0.1)	(0.1)	(0.1)

* Normalized to 300-mg dose.
† Equivalent to intrinsic clearance.
Values are expressed as mean ± standard deviation.
AUC = area under the concentration-vs-time curve; C_{min} = minimal ("trough") concentration; C_{max} = maximal ("peak") concentration; CL_o = oral clearance; $t_{1/2\beta}$ = terminal elimination half-life; T_{max} = time of peak concentration; V_D = volume of distribution.

were based on blood collections taken on the seventh day of each period. Blood collections to determine trough moricizine concentrations, C_{min}, were taken on days 6, 8, 13, 15, 20, 22, 27 and 29. The resulting data, which demonstrate dose proportionality over the dose range studied, are listed in Table I.

In the prior review of pharmacokinetic data,[1] it was pointed out that the steady-state level achieved with multiple dosing is less than that predicted on the basis of the terminal elimination rate constant, suggesting the possibility of increased clearance, decreased plasma protein binding, or both. This was investigated further in another recent unpublished multiple-dose study.*

This was a double-blind study with randomized assignment of subjects to 1 of 2 treatment groups. On day 1, all subjects received a 500-mg oral dose of antipyrine. After a 4- to 6-day washout period, 1 group (n = 6) received a 250-mg oral dose of moricizine hydrochloride every 8 hours for 14 days. The second group (n = 6)

*Du Pont study N-73, data on file, Du Pont Pharmaceuticals.

TABLE II Effects of Moricizine on Antipyrine Disposition After Multiple Dose Administration

Parameter	Before Moricizine	1 Week Moricizine	2 Weeks Moricizine
	Group 1 (2 Weeks of Moricizine)		
C_{max} (mg/L)	9.69 ± 1.0	9.50 ± 2.02	8.74 ± 1.75
T_{max} (hr)	1.0	0.75	0.75
	(0.5–1.0)[a]	(0.5–1.0)[a]	(0.5–1.0)[a]
AUC (mg/L/hr)	132.07 ± 13.39	105.86[e] ± 15.32	90.45[efg] ± 12.89
Cl_o (ml/min/kg)	0.78 ± 0.13	0.98[e] ± 0.14	1.15[eg] ± 0.20
V_D[c] (L/kg)	0.63 ± 0.07	0.66 ± 0.04	0.70 ± 0.06
$T_{1/2\beta}$[d] (hr)	9.3 ± 0.9	7.8 ± 0.9	7.1 ± 0.8
Parameter	Before Moricizine	1 Week Moricizine	1 Week Moricizine, 1 Week Placebo
	Group 2 (1 Week of Moricizine)		
C_{max} (mg/L)	11.50 ± 1.51	10.94 ± 0.84	10.43 ± 0.87
T_{max} (hr)	0.75	0.75	0.75
	(0.5–1.0)[a]	(0.5–1.0)[a]	(0.5–1.0)[a]
AUC (mg/L/hr)	168.20 ± 30.82	120.08[e] ± 20.40	149.24[ef] ± 25.52
Cl_o[b] (ml/min/kg)	0.70 ± 0.12	0.98[e] ± 0.15	0.78[e] ± 0.13
V_D[c] (L/kg)	0.64 ± 0.05	0.65 ± 0.06	0.72 ± 0.12
$t_{1/2\beta}$[d] (hr)	10.5 ± 1.5	7.7[e] ± 1.0	10.4[f] ± 1.6

[a] Range; [b] intrinsic clearance; [c] volume of distribution during terminal phase elimination; [d] harmonic mean; [e] $p < 0.05$ vs day 1 control; [f] $p < 0.05$ vs day 14 control; [g] $p < 0.05$ vs placebo control group 2 day 21.
Values are expressed as mean ± standard deviation.
Abbreviations as in Table I.

TABLE III Moricizine Pharmacokinetics After Repeated Doses

Parameter	1 Day Moricizine	13 Days Moricizine
C_{max} (mg/L)	0.55 ± 0.23	0.39 ± 0.16
T_{max} (hr)	1.0 (0.75–1.0)*	0.75 (0.75–1.5)*
AUC† (mg · hr/L)	1.25 ± 0.59	0.79 ± 0.34
Cl_s (L/hr/kg)	3.08 ± 1.80	4.66 ± 2.28
V_D (L/kg)	5.93 ± 3.22	11.60 ± 6.71
$t_{1/2}$ (hr)‡	1.3 ± 0.1	1.6 ± 0.2

* Median (range).
† $AUC_{0-\infty}$ on day 1 and AUC_{0-8hr} on day 13.
‡ Harmonic mean ± standard deviation.

TABLE IV Mean Serum Digoxin Concentrations During Co-administration of Placebo or Moricizine

	No. of Pts.	Digoxin (ng/ml)
Placebo, baseline	13	0.91 ± 0.12
Moricizine, 1 week	13	1.13 ± 0.16
Moricizine, 2 weeks	13	1.06 ± 0.14
Placebo 1 week after moricizine	7	0.83 ± 0.27

Adapted from *Am Heart J.*[5]

TABLE V Effect of Cimetidine on Moricizine Pharmacokinetics

	Moricizine	Moricizine with Cimetidine
$AUC_{0-\infty}$ (μg/ml/hr)	5.6 ± 1.3	7.8 ± 1.2
Cl_s (ml/min/kg)	38.2 ± 10.7	19.7 ± 4.2
$T_{1/2\beta}$ (hr)	3.4 ± 0.5	4.6 ± 0.5
V_D (L/kg)	11.1 ± 3.1	8.2 ± 1.2

Values are expressed as mean ± standard error of the mean.
$AUC_{0-\infty}$ = area under the moricizine concentration-vs-time curve; other abbreviations as in Table I.
Adapted from *Clin Pharmacol Ther.*[3]

received the 250-mg oral dose every 8 hours for 7 days and placebo treatment for the next 7 days. Subjects from each group each received a second single oral 500-mg antipyrine dose on day 14, coincident with the treatment protocol dose (moricizine or placebo). A third 500-mg antipyrine dose was given on day 21. Blood samples were obtained at appropriate times to determine pharmacokinetic parameter values from moricizine and antipyrine. The data in Table II show that moricizine increased antipyrine clearance and, as seen in Table III, it appeared to have an autoinducing effect in that its own clearance was increased.

DRUG INTERACTIONS

Digoxin: Potential interactions between moricizine and digoxin have been examined in studies involving both normal volunteers and patients. In a study of digoxin pharmacokinetics after a single intravenous dose, MacFarland et al[4] found no difference between values observed at baseline and those noted after steady-state administration of moricizine (12 mg/kg/day in 3 divided doses). Co-administration of digoxin and moricizine caused a significant increase in the PR interval.*

In a study of moricizine efficacy for suppression of chronic ventricular ectopy in patients concomitantly receiving digoxin (for congestive heart failure or atrial fibrillation), Kennedy et al[5] measured digoxin concentrations before, during and after 2 weeks of treatment with moricizine (approximately 10 mg/kg/day in divided doses). No significant changes in digoxin concentration were noted at dosages producing satisfactory suppression of ventricular ectopy (Table IV).

Moricizine frequently increases the PR interval and QRS duration, and there are reports of first-degree atrioventricular block or bundle branch block developing in patients during concomitant digitalis administration.* The known effects of moricizine on calcium conductance may explain the effects on atrioventricular node conduction, whereas its effects on fast sodium current appear responsible for intraventricular conduction abnormalities.

In summary, there does not appear to be a pharmacokinetic interaction between digoxin and moricizine, but the additive effects of the 2 drugs on intranodal and

*Data on file, Du Pont Pharmaceuticals.

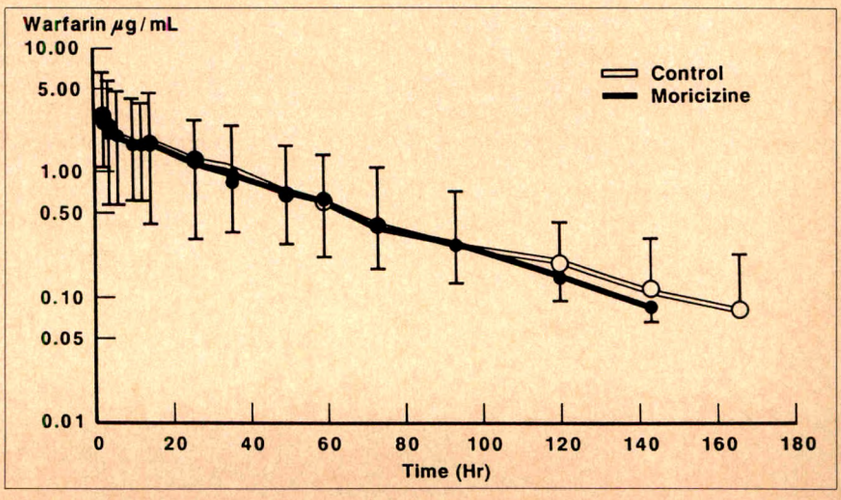


FIGURE 2. Plasma concentration-vs-time curve after a single oral dose of warfarin at baseline and during moricizine administration.

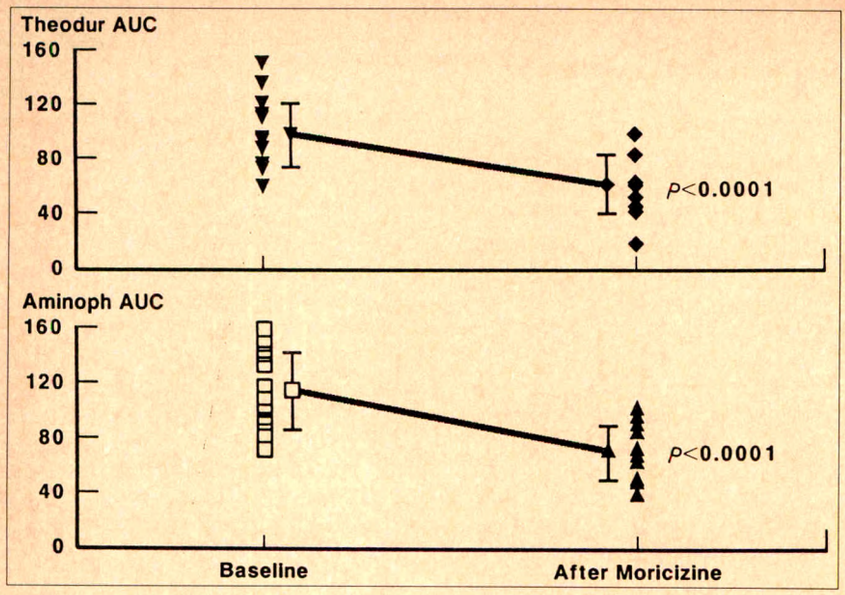


FIGURE 3. Effects of moricizine on area under the curve (AUC) of theophylline after administration of 2 different formulations, anhydrous theophylline (TheoDur®) and aminophylline (Aminoph).

intraventricular conduction may be excessive in some patients with cardiac disease.

Warfarin: The disposition kinetics of warfarin after single-dose administration (25 mg orally) was examined in 12 normal subjects before and after multiple doses of moricizine (250 mg every 8 hours for 14 days).* There was no change in warfarin oral clearance, volume of distribution or plasma protein binding during moricizine administration. There was a slight but statistically significant decrease in warfarin elimination half-life (from 37.6 ± 7.8 to 34.2 ± 4.4 hours) (Fig. 2). There was no change in prothrombin time.

Experience with moricizine in patients chronically receiving warfarin is available. Of 51 patients receiving the 2 drugs together, paired prothrombin time data are available for 34 patients.* There was no significant change in warfarin dosage requirement after initiation of moricizine therapy. Therefore, the clinical experience indicates that there is not a significant pharmacokinetic or pharmacodynamic interaction between moricizine and warfarin.

Propranolol: A potential pharmacokinetic interaction between moricizine and propranolol has not been fully evaluated. Among patients studied to date, there has been no evidence of an adverse drug interaction or significant change in blood pressure or heart rate when the 2 drugs were combined.[6,7]

Cimetidine: Cimetidine is well known for its ability to inhibit hepatic microsomal oxidative enzymes. One would predict that extensively metabolized drugs such as moricizine might have altered pharmacokinetics when combined with cimetidine. As predicted, Biollaz et al[3] found a mean reduction of moricizine clearance of 48% after cimetidine (300 mg 4 times a day for 1 week). The mean half-life increased by 35% (from 3.4 ± 0.5 to 4.6 ± 0.5 hours), and area under the concentration-vs-time curve (AUC) increased by 39% (Table V). There was considerable variability in the extent of cimetidine-induced reduction in moricizine clearance, with the largest effect seen in those subjects with the highest initial values for oral clearance and the lowest initial plasma moricizine concentrations. Despite the striking changes in moricizine concentration and disposition kinetics, there was no significant difference in electrocardiographic intervals. This observation supports the hypothesis that some metabolites of moricizine are active and contribute to the pharmacologic effects during moricizine therapy. This also implies that monitoring plasma moricizine concentrations will be of limited value during therapy.

A pharmacokinetic interaction between ranitidine and moricizine is unlikely, but possible because the effects of ranitidine on liver blood flow might reduce clearance. However, such an effect should be no larger than that seen with cimetidine and should also lack clinical relevance.

Theophylline: A pharmacokinetic interaction between theophylline was suggested by the observation that theophylline levels decreased in 4 patients taking theophylline for asthma and moricizine for arrhythmias.* A complete prospective trial was subsequently performed in 15 normal subjects.* On separate days, single doses of anhydrous theophylline and sustained-release theophylline (TheoDur®) were given and plasma samples collected to characterize the pharmacokinetic profiles for each formulation. After 2 weeks of moricizine administration, the studies were repeated. Major but variable changes in the AUC, oral clearance and half-life occurred with each theophylline formulation, but were greater for the sustained release preparation. Figure 3 demonstrates the changes in the AUC for the 2 formulations before and after moricizine, indicating decreased theophylline available after treatment with moricizine. Moricizine increased theophylline clearance by 46 to 68% and decreased theophylline elimination half-life by 20 to 34%.

*Data on file, Du Pont Pharmaceuticals.

This interaction is very likely to alter the clinical efficacy of theophylline therapy, and therefore theophylline levels should be monitored carefully when the drugs are used together.

This interaction and the evidence that moricizine concentrations in plasma decrease during chronic therapy indicate that drug-metabolizing enzymes can be induced by moricizine. This has also been observed in animal studies* and in the previously described study summarized in Table II. The selective induction of specific antipyrine metabolic pathways implies that there may be other interactions that could occur unpredictably.

*Data on file, Du Pont Pharmaceuticals.

REFERENCES

1. Woosley RL, Morganroth J, Fogoros RN, McMahon G, Humphries JO, Mason DT, Williams RL. Pharmacokinetics of moricizine HCl. *Am J Cardiol 1987;60:35F–39F.*

2. Piotrovski VK, Merkulova IN, Romina NN, Metelista VI. Pharmacokinetics of ethmozine after a single intravenous injection. *Kardiologiia 1982;22:75–80.*

3. Biollaz J, Shaheen O, Wood AJJ. Cimetidine inhibition of ethmozine metabolism. *Clin Pharmacol Ther 1985;37:665–668.*

4. MacFarland RT, Moeller VR, Pieniaszek HJ Jr, Whitney CC Jr, Marcus FI. Assessment of the potential pharmacokinetic interaction between digoxin and ethmozine. *J Clin Pharmacol 1985;25:138–143.*

5. Kennedy HL, Sprague MK, Redd RM, Wiens RD, Blum RI, Buchingham TA. Serum digoxin concentrations during Ethmozine therapy. *Am Heart J 1986;111:667–672.*

6. Pratt CM, Butman SM, Young JB, Knoll M, English LD. Antiarrhythmic efficacy of ethmozine (moricizine HCl) compared with disopyramide and propranolol. *Am J Cardiol 1987;60:52F–58F.*

7. Butman SM, Knoll ML, Gardin JM. Comparison of ethmozine to propranolol and the combination for ventricular arrhythmias. *Am J Cardiol 1987;60:603–607.*

Dose Effect of Moricizine on Suppression of Ventricular Arrhythmias

Joel Morganroth, MD

To define the pharmacologic properties of moricizine in patients with benign or potentially lethal ventricular arrhythmias, 1,072 patients in the moricizine data base through February 1987 were evaluated. In dose-ranging and titration trials as well as in a cross-study analysis of the entire data base, the minimally effective dose for moricizine was found to be 600 mg/day and the optimal dose range from 600 to 900 mg/day. The dose efficacy relation plateaued beyond 900 mg/day. With use of a 75% reduction in ventricular premature complex frequency as the definition of a drug responder, 391 of 583 patients (67%) with paired Holter monitors demonstrated overall efficacy. The dose onset of moricizine was between 16 and 20 hours and the dose offset was at approximately 24 hours at the point when 50% of the ventricular arrhythmia frequency returned to baseline. Although moricizine was primarily given on a 3-times-a-day regimen during clinical trials, dose interval evaluation suggested that a twice-a-day regimen may produce the same degree of efficacy although there are limited data regarding comparable safety.

(Am J Cardiol 1990;65:26D–31D)

From the Departments of Medicine & Cardiovascular Diseases, The Graduate Hospital and the University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

Address for reprints: Joel Morganroth, MD, Center of Excellence for Cardiovascular Studies, The Graduate Hospital, One Graduate Plaza, Philadelphia, Pennsylvania 19146.

Antiarrhythmic drugs are prescribed by physicians to prevent or eliminate clinically important ventricular arrhythmias.[1,2] Because any therapeutic agent is potentially toxic, physicians should always seek the minimally effective dose required to reach the desired therapeutic end point. In addition, the proper dose interval of the therapeutic agent should be clearly established to eliminate any periods of inefficacy or potential adverse effects due to unnecessarily high peak drug concentration. During new drug development, careful clinical trials should be conducted to establish both dose-effect relations, onset of therapeutic action, offset of action and the proper interdose interval.

This report describes the data from the moricizine new drug application data base that were used to establish these important pharmacologic variables.

METHODS

Study population: The moricizine new drug application data base (as of February 1987) evaluated 1,072 people treated with moricizine for ventricular arrhythmias. This population consisted of 99 patients (9%) with benign, 576 (54%) with potentially lethal and 397 (37%) with lethal ventricular arrhythmias.[1] Concomitant cardiovascular agents were administered to 856 of 1,072 patients (80%). These included diuretic drugs in 535 (50%), vasodilators in 488 (46%), cardiac glycosides in 445 (42%), calcium channel blockers in 183 (18%), β blockers in 175 (16%) and additional antiarrhythmic therapy in 131 (12%). Figure 1 displays the cardiovascular history of these 1,072 adults treated with moricizine for ventricular arrhythmias. Almost all of these patients had underlying cardiovascular disease with over one-half having a history of myocardial infarction and only 7% having no structural cardiovascular disease with ventricular arrhythmias, so-called idiopathic ventricular ectopic activity.

Arrhythmia monitoring methods: To evaluate suppression of ventricular premature complexes (VPCs) or nonsustained ventricular tachycardia (VT), electrocardiographic monitoring (Holter monitoring) was performed. To qualify for inclusion in the dose-effect analysis, patients had to have at least one 24-hour Holter monitor recording before institution of moricizine therapy, and at least one 24-hour Holter monitor recording with moricizine at a known dosage. A minimum of 18 of 24 hours of high quality electrocardiographic data was necessary for that Holter to be a qualified study. To qualify for entry and moricizine dosing, patients had to have at least 30 VPCs/hour on average at baseline. The

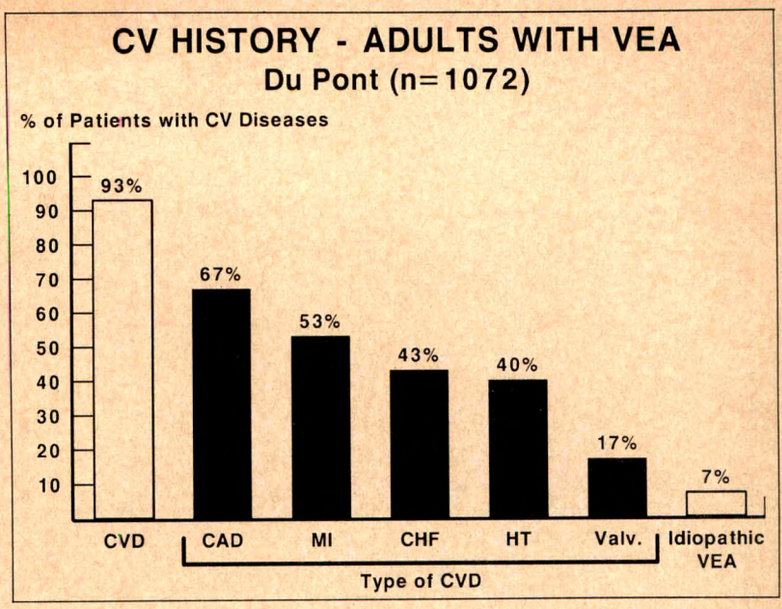


FIGURE 1. The cardiovascular (CV) history of the adult patients treated with moricizine for ventricular ectopic activity (VEA) in the Du Pont-sponsored data base is depicted. CAD = coronary artery disease; CHF = congestive heart failure; HT = hypertension; MI = myocardial infarction; Valv. = valvular heart disease.

effect of moricizine on the suppression of VPCs was based on the median or geometric mean percent change on moricizine compared with baseline. In addition, drug effect was evaluated as the percent of responders taking moricizine. A responder was defined as one who demonstrated at least a 75% reduction in mean VPCs per hour with moricizine at a particular dose compared with baseline. A responder for nonsustained VT was defined when at least a 90% reduction in the number of beats in the form of nonsustained VT occurred with moricizine compared with baseline.

RESULTS

In interrogating the entire moricizine data base, 583 patients had paired Holter monitoring for evaluation. The number of Holter recordings per patient ranged from 2 to 54 (mean 13).

Dose effect relations: The initial evaluation of moricizine was conducted in 2 separate protocols in hospitalized patients with benign or potentially lethal ventricular arrhythmias. The first trial included a 5-center evaluation of moricizine (study numbers N5 through N9) in which 73 patients underwent therapy with a fixed daily moricizine dose of 300 to 900 mg/day given 3 times a day over 7 days after an initial 3 days of placebo baseline monitoring to establish entry criteria.[3] The second protocol involved 2 sites (N39 and N47) in which 16 patients were dosed with moricizine from 900 to 1,650 mg/day given 3 times a day for 10 days after a 2- to 3-day placebo baseline. These patients also were continuously monitored in the hospital. This single-blind placebo-controlled protocol demonstrated overall that median VPC frequency was reduced 66% in studies N5 through N9 and 96% in N39 and N47 at the higher doses of moricizine. Figure 2 shows the dose-response relation derived from the data from these 2 types of studies. The geometric mean percent reduction in

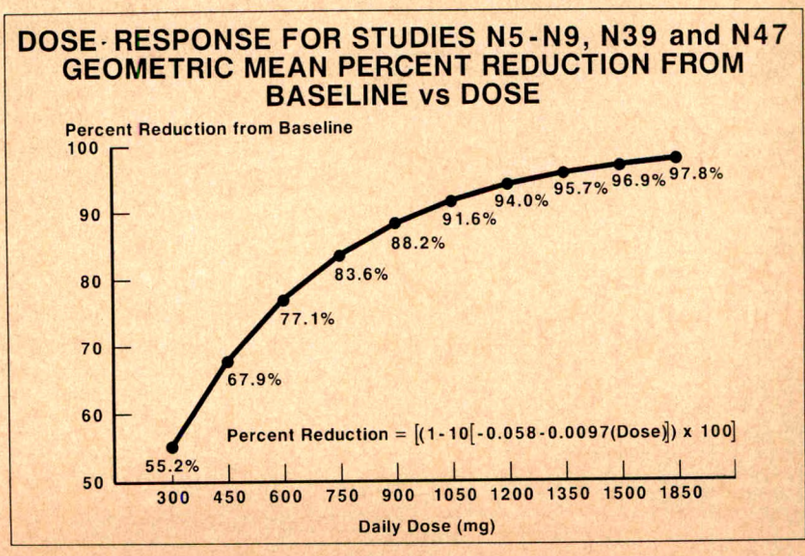


FIGURE 2. The dose response for the early dose findings in single-blind placebo-controlled trials (at study sites N5–N9, N39 and N47) is depicted in which the percent reduction from baseline in geometric mean for ventricular premature complexes compared with the daily dose of moricizine is demonstrated.

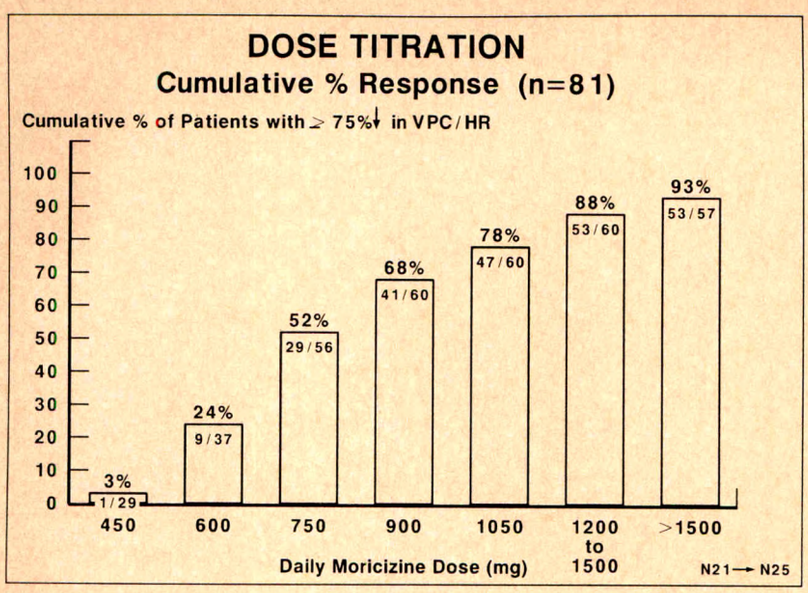


FIGURE 3. The dose-titration response from the titration study at 5 sites N21 through N25 is depicted for 81 patients. A cumulative percent response (responders carry forward) for patients who reached at least a 75% reduction in ventricular premature complexes (VPCs) with the drug compared with baseline are shown. These data show that the daily moricizine optimal dose range is from 600 to 900 mg/day.

VPCs from baseline is compared with the daily fixed dose of moricizine. These data document a progressive dose-response relation for moricizine and suggest that doses less than 600 mg/day would be considered suboptimal with the minimally effective dose at 600 mg/day and the optimal range between 600 to 900 mg/day.

In these 2 trials comprising a total of 89 patients, 23 patients received 300 to 450 mg/day and 17% were defined as responders. Among the 51 patients receiving 600 to 900 mg/day, 57% were declared responders and in the 15 patients administered more than 900 mg/day, 73% were defined as responders.

A formal dose titration study was conducted (study numbers N21 to N25) in 5 sites comprising 88 patients using a single-blind, placebo-baseline-controlled outpatient design. After three 24-hour Holter monitoring sessions during a 1-week placebo period, qualified patients were then given low, then medium, then high doses of moricizine depending on the VPC frequency response (48 hours of Holter monitoring) at the end of each week of dosing. Patients received a fixed dose of moricizine based on body weight. Figure 3 details the cumulative percent response rate in this titration study and again documents the optimal dose range of 600 to 900 mg/day with little efficacy below 600 mg/day.

TABLE I Cumulative Dose Effect Relation of Moricizine

Daily Dose (mg)	Dose Response* (n = 89)	Cumulative Percent Responders: Titration N21–N25 (n = 81)	Titration CAPS (n = 98)	Entire Data Base VPCs (n = 583)	Entire Data Base NSVT (n = 332)
300	4	—	—	2	2
450	10	3	—	3	6
600	49	24	52	29	28
750	74	52	66	56	60
900	85	68	—	76	83
1,050	90	78	—	90	92
1,200	93	88	—	96	95
>1,200	98	93	—	99	—

* N5–N9; N39 and N47.
CAPS = Cardiac Arrhythmia Suppression Trial; NSVT = nonsustained ventricular tachycardia; VPCs = ventricular premature complexes.

Cumulative dose response analysis: A cross-study analysis was performed on the entire moricizine data base in 583 patients who had VPCs and at least one 24-hour Holter recording at baseline and one 24-hour Holter recording with moricizine therapy. Three hundred ninety-one of these 583 patients (67%) were declared responders, having met the criteria of at least a 75% reduction in VPC frequency with moricizine compared with baseline. After analyzing these data by carrying forward all patients as responders receiving higher doses whether or not they received that higher dose and carrying backward all non-responders to lower doses whether or not they received that lower dose, Table I details the cumulative dose-effect relation. These data for the entire data base are compared with the initial dose response (N5 through N9, N39 and N47) and titration data (N21 through N25), as well as the Cardiac Arrhythmia Pilot Study, which was a parallel, placebo-controlled trial in postmyocardial infarction patients who received 600 and 750 mg/day of moricizine.[4] The data again indicate that the optimal dose range for moricizine appears to be between 600 and 900 mg/day, with little efficacy below 600 mg/day and with some increase in efficacy greater than 900 mg/day.

In addition, an analysis was conducted on 332 patients with nonsustained VT in which the percent of patients responding was defined using at least a 90% reduction in nonsustained VT frequency with the drug compared with baseline. Once again, the 600 to 900 mg/day schedule appears to be optimal.

Dose onset of moricizine: To evaluate the dose onset of moricizine, patients with ventricular arrhythmias in the entire data base were extracted who had had a 24-hour Holter recording on the first day of moricizine dosing. Because this was a retrospective analysis, some patients may not have had Holter monitoring data during

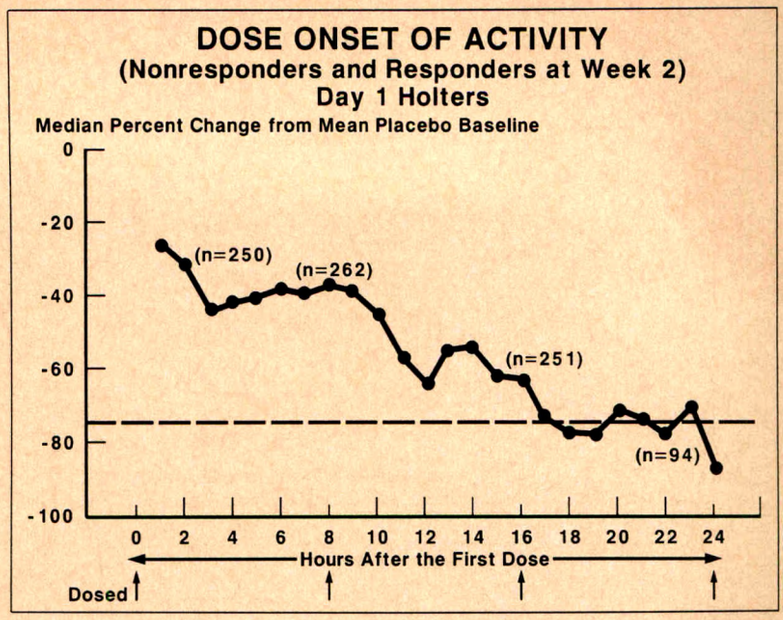


FIGURE 4. The dose onset of activity of moricizine in nonresponders and responders at week 2 (a responder is one who reached at least a 75% reduction in ventricular premature complexes per hour) is shown for patients who had Holter recordings on the first day of moricizine dosing. Dosing was on a 3-times-a-day basis at (0, 8, 16 and then again at 24 hours). The onset of antiarrhythmic activity, defined as at least a 75% median percent reduction, occurs after 16 hours.

the first few hours of moricizine therapy on day 1 of therapy and some Holter recordings may not have lasted a full 24 hours. Figure 4 details the data which demonstrate in nonresponders and responders at week 2 of moricizine therapy that the onset of moricizine activity (as judged by the medium percent change in VPC frequency from baseline) appears to occur between 16 and 20 hours after initiation of therapy. Thus, when starting moricizine for patients with ventricular ectopic activity, one would not expect to see a significant suppression of VPCs until at least the latter half of the first day of dosing.

Dose offset of moricizine: To evaluate the dose offset of moricizine, patients enrolled in the formal titration studies who had a Holter monitor placed immediately after discontinuation of moricizine that ran for at least 48 hours were retrospectively collected. Data were available for this analysis from the titration studies at centers N9, N39 and N47 and from center N41 which evaluated the dose interval for moricizine (see later). These inclusion criteria were met in 26 responders. Figure 5 shows the percent of baseline VPC frequency that was reached with regard to the time after discontinuation of moricizine. More than 24 hours elapsed before at least 50% of baseline VPC frequency reoccurred.

Time interval for moricizine dosing: A single-blind placebo-controlled crossover study in 24 patients was conducted at 2 centers (study numbers N41 and N45) in which patients after a 1-week placebo baseline underwent 48 hours of Holter monitoring to determine if at least 30 VPCs/hour were present. Qualifiers were randomized to receive a fixed dose of moricizine based on body weight for 1 week either as 2- or 3-times-a-day regimen.[5] After a

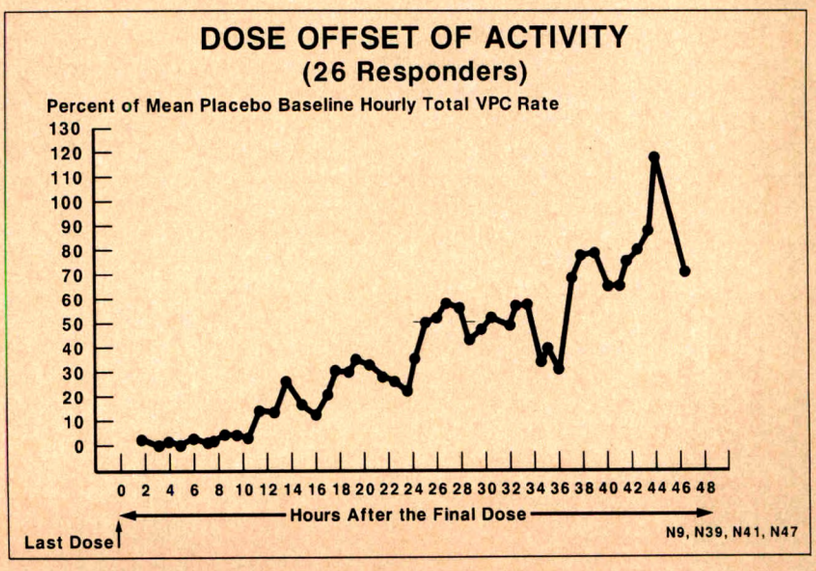


FIGURE 5. The dose offset of activity of moricizine is demonstrated in 26 responders from the early dose-ranging trials (N9, N39 and N47) as well as the dose interval trial site N41. Twenty-six responders were found who had at least 48 hours of Holter monitoring after receiving their last dose of moricizine. The dose offset appears to occur at approximately 24 hours when 50% of mean hourly ventricular premature complexes (VPCs) have returned to the baseline frequency.

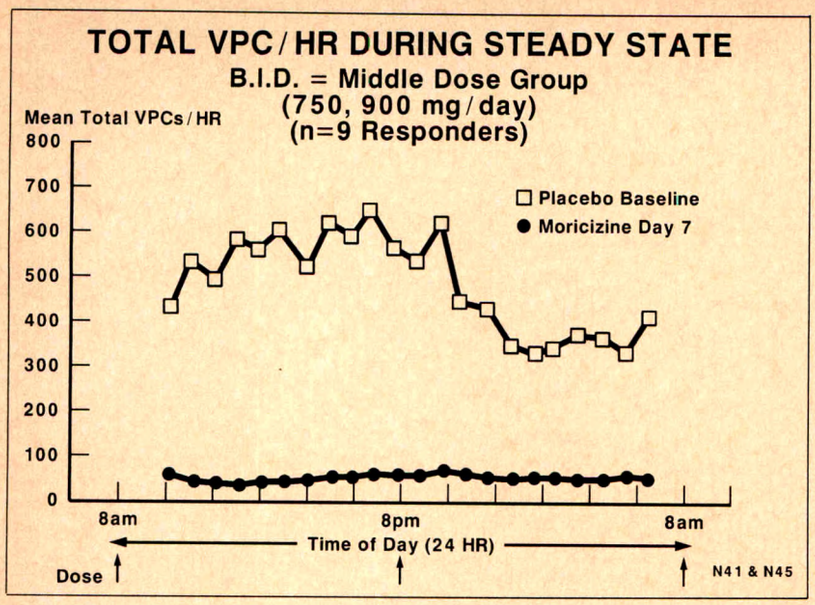


FIGURE 6. The 9 responders in the dose interval (study sites N41 and N45) who received moricizine on a twice-a-day basis (B.I.D.) were demonstrated in which total ventricular premature complexes (VPCs) per hour are plotted against the hourly VPC frequency for moricizine at day 7 of therapy compared with the placebo period. The data demonstrate that in these patients the twice-a-day regimen was not correlated with any breakthrough in VPC frequency.

1-week washout, patients were crossed over to the alternate dosing regimen. Holter monitoring was obtained for at least 48 hours to judge therapeutic effect. Of the 24 patients who entered this trial, 17 completed the 3-times-a-day dosing schedule and 18 the 2-times-a-day schedule. Overall, 71% of patients responded on the 3-times-a-day vs 75% on the 2-times-a-day regimen. The mean percent of VPC reduction was 90% for the 3-times-a-day arm and 95% for the 2-times-a-day arm.

Figure 6 details the hour-to-hour VPC frequency among the responders in the optimal dose group compared with the placebo baseline. These data show that there was no evidence of change in VPC frequency at the end of every 12-hour dosing interval, suggesting that moricizine may be effective as a twice-a-day agent although most of the patients in the data base were given a 3-times-a-day regimen.

DISCUSSION

Evaluation of the pharmacologic properties of antiarrhythmic drugs in patients with ventricular ectopic activity requires establishment of careful dose effect relations. The data in this manuscript have described the optimal dose range, dose onset, dose offset and dosing interval for moricizine in patients with benign or potentially lethal ventricular arrhythmias. Early dose ranging, single-blind, placebo-controlled trials demonstrated that the minimal effective dose of moricizine appears to be 600 mg/day with increasing efficacy as the dose is increased.[3,6] This increasing efficacy begins to plateau after 900 mg/day. Thus, the optimal dose range for moricizine appears to be between 600 and 900 mg/day. Although no formal parallel placebo-controlled dosing study was performed in this data base, a study design that probably is the most effective way of demonstrating dose effect relations,[7] the data from the titration studies and the total data base cross-study analysis (Table I) were all confirmatory in establishing 600 to 900 mg/day as the optimal dose range for moricizine. When these data were compared with data from The Cardiac Arrhythmia Suppression Trial,[4] a parallel placebo-controlled data base, the comparable dose range was demonstrated. Overall, the efficacy of moricizine in 583 patients with paired Holter monitoring data was 67%, which is quite comparable for quinidine in similar populations and more effective than class IB and II antiarrhythmic agents.[8]

The onset of moricizine's antiarrhythmic action appears to be about 16 to 20 hours after initiating therapy on a 3-times-a-day basis. Because moricizine is highly metabolized in the liver to many metabolites, some of which are probably active, the full antiarrhythmic effect of this agent appears to require this biotransformation.[9] Similarly, the offset of effect of moricizine appears to occur after many hours to perhaps a day or more, again suggesting that the active metabolites have a prolonged biologic half-life.

In patients with symptomatic ventricular arrhythmias requiring antiarrhythmic drug suppression, compliance is always an important issue. The data from the dose-interval trials suggest that moricizine is as effective when given twice a day or 3 times a day.[5] This finding is consistent with the possibility of a prolonged biologic half-life for the active metabolites. More data are needed to evaluate the relative safety of 2- vs 3-times-a-day moricizine use, particularly since most of the safety data in the moricizine data base were derived from the 3-times-a-day dosing schedule.

The data described in this manuscript cannot be necessarily extrapolated to patients with other forms of ventricular arrhythmias such as malignant ventricular tachyarrhythmias or to patients with supraventricular arrhythmias. Antiarrhythmic drugs must be evaluated separately in these populations because it is often found that lower doses of the antiarrhythmic drug are necessary

to maintain a favorable efficacy vs safety balance, particularly in treating patients with more serious ventricular tachyarrhythmias.[10]

REFERENCES

1. Morganroth J. Premature ventricular complexes: diagnosis and indications for therapy. *JAMA 1984;252:673–676.*

2. Bigger JT. Identification of patients at high risk for sudden cardiac death. *Am J Cardiol 1984;54:3D–8D.*

3. Morganroth J, Pearlman AS, Kunkman WB, Horowitz LN, Iuephsa ME, Michelson EL. Ethmozine: a new antiarrhythmic agent developed in the USSR: efficacy and tolerance. *Am Heart J 1979;98:621–628.*

4. The Cardiac Arrhythmia Pilot Study (CAPS) Investigators. Effects of encainide, flecainide, imipramine and moricizine on ventricular arrhythmias during the first year after myocardial infarction: the CAPS. *Am J Cardiol 1988;61:501–509.*

5. Morganroth J. Safety and efficacy of a twice-daily dosing regimen for moricizine (ethmozine). *Am Heart J 1985;110:1188–1192.*

6. Podrid PT, Lyakishev A, Lown B, Mazur N. Ethmozine—a new antiarrhythmic drug for suppressing ventricular premature complexes. *Circulation 1980; 61:450–457.*

7. Morganroth J, Pool P, Miller R, Hsu P, Lee I, Clark DM for the Encainide Research Group. Dose-response range of encainide for benign and potentially lethal ventricular arrhythmias. *Am J Cardiol 1986;57:769–774.*

8. Morganroth J. Ambulatory electrocardiographic monitoring in the evaluation of new antiarrhythmic drugs. *Circulation 1986;73:suppl II:II-92–II-97.*

9. Pieniaszek HJ. Disposition of orally administered 14C-ethmozine in healthy volunteers. *Alpha Academy of Pharmaceutical Sciences. 1984;14:244.*

10. Morganroth J, Anderson JL, Gentzkow, GD. Classification by type of ventricular arrhythmia predicts frequency of adverse cardiac events from flecainide. *JACC 1986;8:607–615.*

Comparisons of Efficacy and Tolerance of Moricizine with Other Antiarrhythmic Agents in the Treatment of Chronic Ventricular Arrhythmias

Jeffrey L. Anderson, MD

Comparative trials of a new drug with standard antiarrhythmic agents are important for establishing relative efficacy and tolerance. For moricizine, such trials have included comparisons with propranolol, disopyramide and quinidine. Furthermore, the Cardiac Arrhythmia Pilot Study compared moricizine in postinfarction patients with encainide and flecainide. These trials show moricizine to be superior in efficacy to a β blocker (propranolol) and disopyramide and equivalent to quinidine. Although the class IC drugs (encainide and flecainide) showed somewhat greater efficacy in the Cardiac Arrhythmic Pilot Study, they are now known to increase the risk of mortality in postinfarction patients. Moricizine was also shown to be well tolerated in these trials and associated with fewer discontinuations than propranolol, disopyramide and quinidine. Thus, moricizine is a promising new agent when profiled against other drugs frequently used for therapy of chronic ventricular arrhythmias.

(Am J Cardiol 1990;65:32D–40D)

From the University of Utah Medical School, LDS Hospital, Salt Lake City, Utah.

Address for reprints: Jeffrey L. Anderson, MD, LDS Hospital, 8th Avenue & C Street, Salt Lake City, Utah 84143.

Comparative trials with placebo and standard agents are critical in new antiarrhythmic drug evaluation for establishing absolute and relative efficacy and tolerance. This report focuses on comparative trials of moricizine with other antiarrhythmic agents.[1–5] These trials have included comparisons with propranolol, disopyramide and quinidine. A further important comparison occurred in the Cardiac Arrhythmia Pilot Study (CAPS),[6,7] in which moricizine was compared with the potent class IC agents encainide and flecainide, and with imipramine, a tricyclic drug with antiarrhythmic properties, in postinfarction patients with prognostically important ventricular arrhythmias. These studies are reviewed to allow profiling of moricizine among other antiarrhythmic drugs and drug classes.

COMPARISON OF THE EFFICACY AND TOLERANCE OF MORICIZINE AND PROPRANOLOL, ALONE AND IN COMBINATION

Propranolol is a prototype β blocker (Vaughan Williams class II) agent that is approved for therapy of chronic ventricular arrhythmias. Propranolol and other β blockers share widespread use for a variety of indications, including hypertension, angina, postmyocardial infarction prophylaxis and antiarrhythmic therapy (both supraventricular and ventricular). A comparison of efficacy and tolerance of new antiarrhythmic agents with β blockers is thus of interest. Evaluation of combination as well as individual therapy is appropriate, given the widespread use of propranolol in antiarrhythmic combinations as well as its other indications in populations of patients who are often candidates for antiarrhythmic drug therapy. Such a study has been performed for moricizine and propranolol.[1]

METHODS

Study design (Fig. 1): A comparison of moricizine and propranolol was conducted in a study in 2 parts (EN/313-N-28).[1] Part I was a double-blind, placebo, baseline-controlled, within-patient, crossover design, comparing moricizine, propranolol, and their combination. The crossover periods consisted of four 1-week placebo periods (weeks 1, 3, 5 and 7) and three 1-week active drug periods (weeks 2, 4 and 6) (Fig. 1). The 3 active treatments were administered in a randomly assigned se-

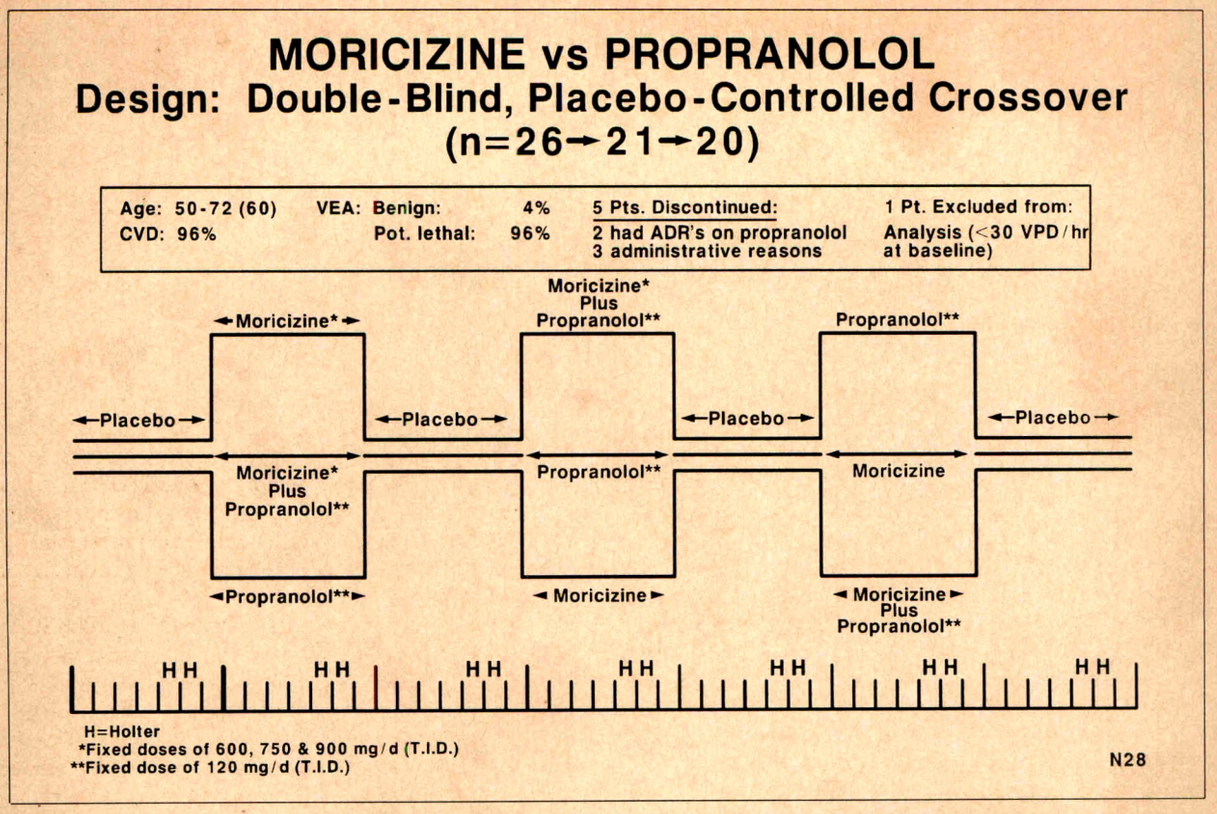


FIGURE 1. Study design for trial comparing moricizine, propranolol, and their combination.[1] ADR = adverse drug reaction; CVD = cardiovascular disease; VEA = ventricular ectopic activity; VPD = ventricular premature depolarization.

quence. A second part consisted of a long-term (to 2 years) evaluation of efficacy and tolerance using an open design. Patients in whom moricizine or moricizine plus propranolol was efficacious and well tolerated in part I were allowed to continue to take the drug and their response during chronic therapy was monitored. Efficacy was defined as ≥75% reduction from baseline in mean frequency of total ventricular premature complexes (VPCs) per hour.

Dose schedule: Study medication was administered 3 times daily (every 8 hours) in equally divided doses. Total daily dosage for propranolol hydrochloride was 120 mg, and for moricizine, 600, 750 or 900 mg, approximating 10 mg/kg/day (range 9.4 to 12 mg/kg/day). Average moricizine dose was 800 mg/day. Doses were divided on a 3-times-a-day basis.

Study group: Twenty-six men (average age 60.4 years, range 50 to 72) with prognostically important ventricular arrhythmias (complex arrhythmias occurring in the setting of organic heart disease, such as coronary artery disease [n = 25]), were entered into the study. Of these, 15 (58%) had previously undergone trials with other antiarrhythmic agents with unsatisfactory results. Of the 26 patients, 21 completed part I, and 20 were analyzable for efficacy during all 3 active treatment periods (in 2, an adverse drug reaction to propranolol forced discontinuation). Sixteen patients entered part II and 8 had data available at 1 month for analysis.

RESULTS

Part I (double-blind, placebo, baseline-controlled, crossover) (Fig. 2): Moricizine had a twofold advantage over propranolol in average decrease in total VPCs per hour and an even greater advantage in the number (%) of patients who achieved the efficacy criterion of ≥75% arrhythmia reduction. Combined therapy was only slightly more effective than moricizine alone. Moricizine achieved an 86% average decrease in total VPCs per hour, propranolol 41% and combined therapy 90%. Fourteen (70%) of the patients treated with moricizine reached or exceeded the 75% efficacy criterion for suppression, compared with only 2 (10%) with propranolol.

Serious adverse reactions occurred more often with propranolol than moricizine. Any adverse experience occurred in approximately one-half of patients during the study (12 of 21 [57%] during moricizine therapy, 10 of 24 [42%] during propranolol therapy, and 11 of 23 [48%] during combination therapy). Discontinuation was required in 2 patients during propranolol therapy, and the 2 patients having proarrhythmia were both receiving propranolol. Mean blood pressure tended to increase during moricizine (7 mm Hg) and decrease during propranolol ($p < 0.05$). Pulse rates also increased slightly after moricizine (+6 beats/min) and decreased after propranolol (−9 beats/min, $p < 0.05$). Combination therapy resulted in a significant reduction in mean pulse rate and blood pressure. Propranolol also tended to decrease cardiac index.

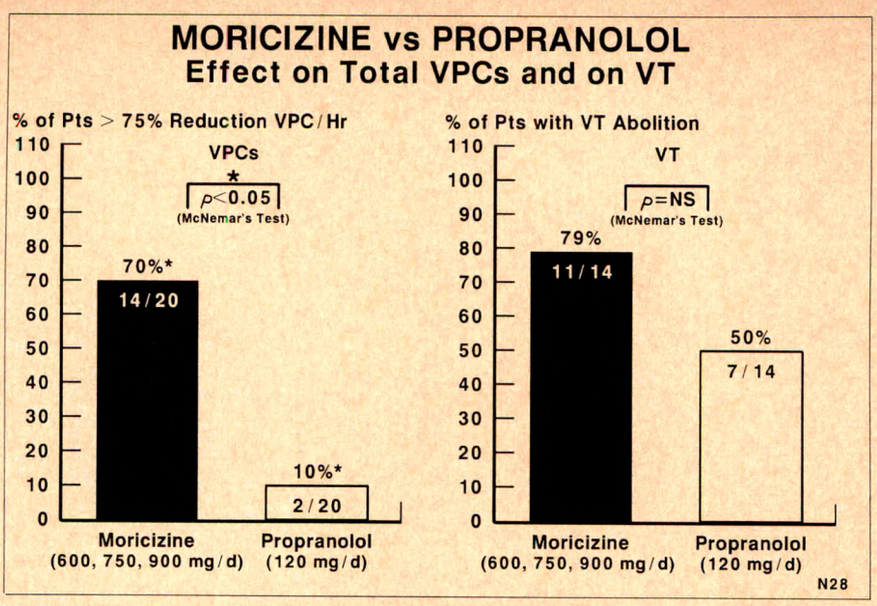


FIGURE 2. Response of ventricular premature complexes (VPCs) to therapy with moricizine, propranolol, and their combination. NS = not significant; VT = ventricular tachycardia.

Moricizine did not significantly affect cardiac index or left ventricular function. Each of the 3 therapies lengthened PR interval within the normal range. Other electrocardiographic intervals did not change with either therapy tested alone; however, mean QRS lengthened somewhat (9 ms) during combined dosing.

Part II (long-term dosing): Data from the open-label dosing experience was limited. In 6 patients receiving moricizine alone, reduction of VPCs averaged 93% at 1 month, 92% at 3 months and 82% at 6 months (n = 5). Two patients completing 1 month of combined therapy had an average reduction in VPCs of 57%. Two other patients died during part II: 1 had an acute myocardial infarction and the other died suddenly because of an ischemia-related cardiac arrhythmia.

Conclusion: Compared with propranolol, a standard β blocker used for therapy of ventricular arrhythmias, moricizine was more effective and caused fewer discontinuations. Concomitant administration of propranolol was safe, added a slight but statistically insignificant increase in efficacy, and moderated the divergent effects on pulse and blood pressure seen with the individual agents alone. The 2 deaths during long-term therapy with moricizine were not believed to be related to therapy.

EFFICACY AND TOLERANCE OF MORICIZINE COMPARED WITH DISOPYRAMIDE FOR NON–LIFE-THREATENING VENTRICULAR ARRHYTHMIAS

Disopyramide is a well-studied class IA antiarrhythmic agent with little organ-toxic potential that is an appropriate comparative standard for studies in patients with non–life-threatening ventricular arrhythmias requiring chronic therapy. Such a comparative study with moricizine (EN/313-N-31) has been performed.[2,3]

METHODS

Study design (Fig. 3): A double-blind, placebo-controlled, within-patient, crossover design was selected to compare the safety and efficacy of orally administered moricizine and disopyramide in outpatients with chronic, non–life-threatening ventricular arrhythmias. The study was a 37-day trial conducted in 4 phases: (1) a 7-day placebo phase, (2) a 10-day dosing phase with the first active drug, (3) a 10-day placebo washout phase, and (4) a 10-day dosing phase on the second active drug. A ≥75% reduction from the preceding placebo baseline phase in mean hourly frequency of total VPCs was used to define a successful clinical response in individual patients. Efficacy was assessed on the last 3 days of each active drug dosing phase (days 8 to 10). The response of paired VPCs and runs of nonsustained ventricular tachycardia (VT) were secondary outcome variables. During dosing, 1 patient discontinued disopyramide and 1 moricizine because of adverse reactions.

Drug dosing: Dosing sequence was randomly distributed between the 2 active drugs. Disopyramide was administered in a total oral daily dose of 600 mg, divided equally into 4 doses given at 6-hour intervals. A total daily dosage of moricizine of either 600, 750 or 900 mg was selected, based on individual patient body weight to approximate 10 mg/kg/day (range 7.4 to 11.2 mg/kg/day). Average dose was 800 mg/day, divided into 3 equal doses.

Study group: Thirty-three outpatients (22 men and 11 women, average age 55.7 years, range 28 to 76) were enrolled. Most patients (n = 22) were symptomatic, and virtually all (n = 32) had associated cardiovascular conditions, including hypertension (n = 15), coronary artery disease (n = 13), previous myocardial infarction (n = 10) or mitral valve prolapse (n = 6). Arrhythmias were clas-

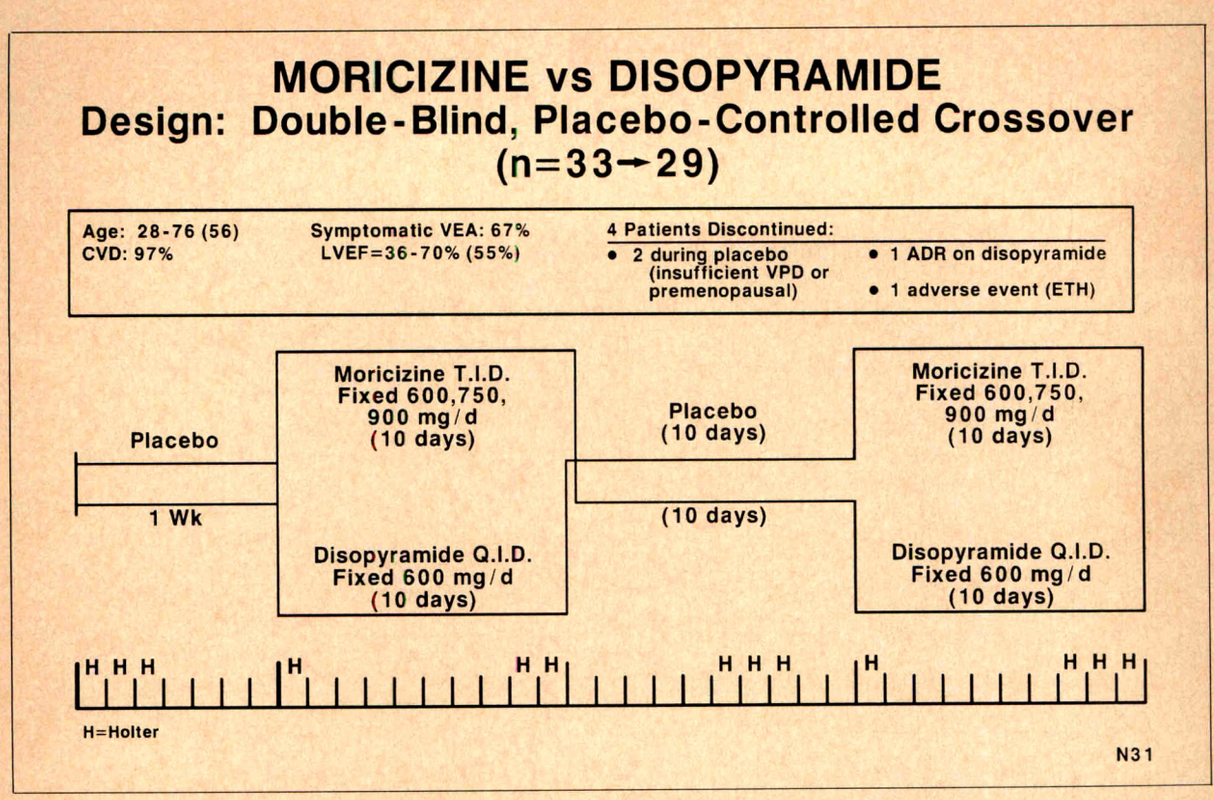


FIGURE 3. Study design for trial comparing moricizine and disopyramide. ETH = ethmozine (moricizine); LVEF = left ventricular ejection fraction; other abbreviations as in Figure 1.

sified as benign (symptomatic) in 5, and prognostically important (potentially lethal) in the others. Twenty-nine patients completed the 4 dosing phases and had data available for complete efficacy analysis. (Two were excluded during the placebo phase because of insufficient arrhythmia or failure to meet entry criteria.)

RESULTS (FIG. 4)

An analysis both of all 29 completing patients (overall or secondary analysis) and of 20 patients who had not had prior exposure to moricizine or disopyramide (restricted or primary analysis) was performed. The efficacy of moricizine was superior to disopyramide both in terms of

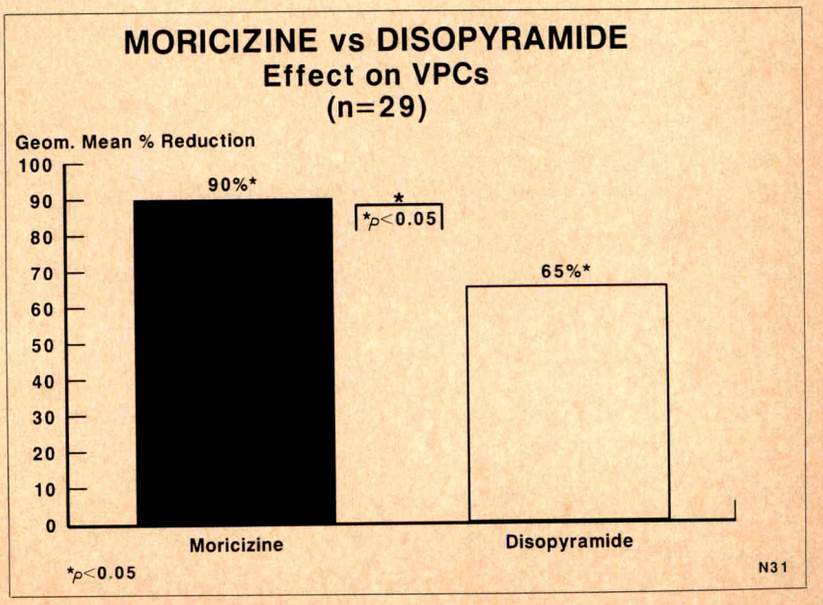


FIGURE 4. Response of ventricular premature complexes (VPCs) to therapy with moricizine vs disopyramide. Geom. = geometric.

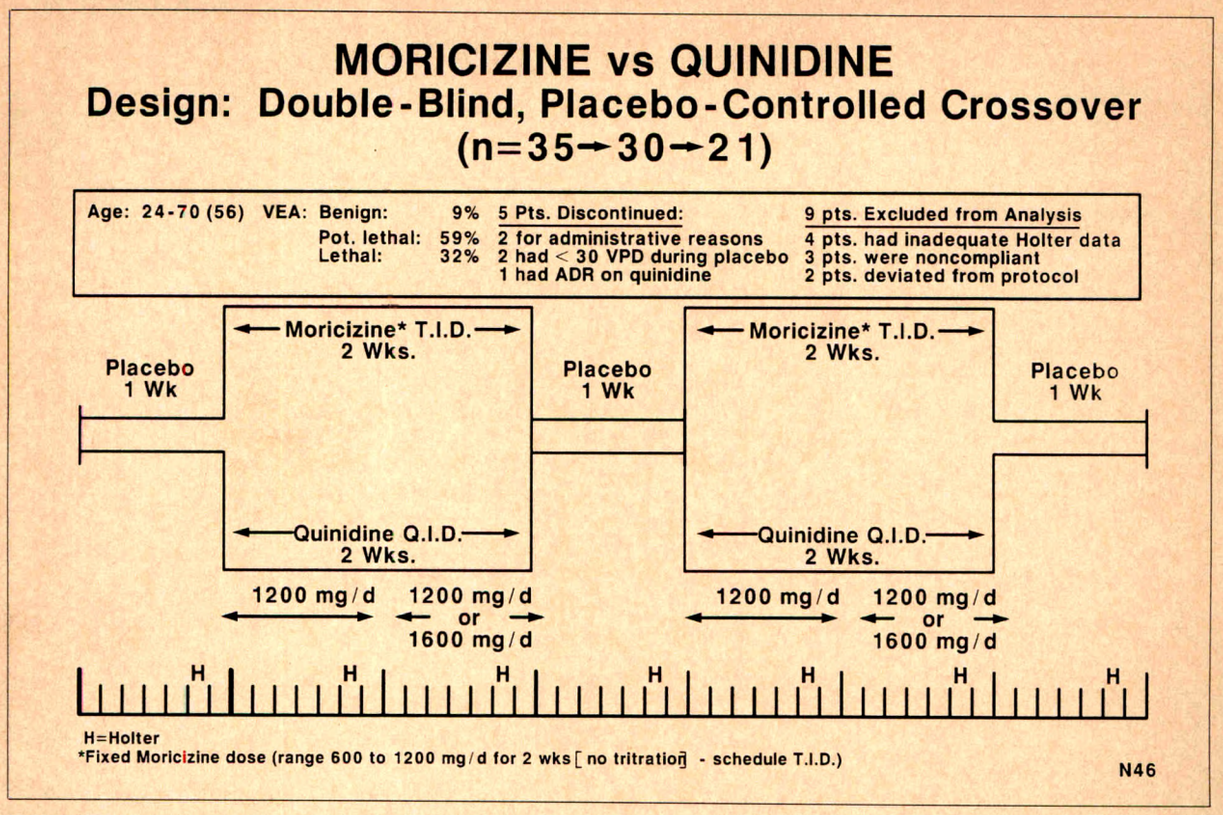


FIGURE 5. Study design for comparison of moricizine and quinidine. Pot. = potentially; other abbrevations as in Figure 1.

average percent VPC reduction and in percent of patients effectively suppressed. Results were similar for the overall (n = 29) and primary (n = 20) patient-based analyses. Reduction in total VPCs per hour averaged 90% for moricizine compared with 65% for disopyramide (n = 29).

A clinical response was obtained in 52% (15 of 29) of patients during moricizine therapy, compared with 31% (9 of 29) during disopyramide. Suppression of paired VPCs averaged 81 and 78%, respectively. Nonsustained VT was abolished in 67 and 65% of patients, respectively.

No deaths occurred during the study. Two patients discontinued therapy because of adverse experiences: 1 during disopyramide therapy because of urinary retention and 1 during moricizine therapy because of exacerbation of preexisting congestive heart failure (considered to be nondrug related). Subjective complaints were registered by substantially more patients during disopyramide (18 = 58%) than during moricizine dosing (6 = 20%). Neither drug produced clinically significant hemodynamic or functional changes (assessed echocardiographically). Blood pressure and pulse rates increased slightly during administration of moricizine. Disopyramide decreased pulse rate slightly. Ventricular repolarization (QTc interval) was prolonged with disopyramide but shortened slightly during moricizine therapy.

Conclusions: Compared with disopyramide (dose 600 mg/day), moricizine (800 mg/day) produced a significantly greater reduction in chronic ventricular arrhythmias and was associated with a lower incidence of drug-related adverse effects.

COMPARISONS OF MORICIZINE WITH QUINIDINE IN PATIENTS WITH NON–LIFE-THREATENING VENTRICULAR ARRHYTHMIAS

Quinidine, the oldest and most widely used antiarrhythmic represents an important standard for comparison with new antiarrhythmic agents. Because quinidine has served as a comparative standard for all recently developed antiarrhythmic drugs, it can also be used as an indirect index of efficacy and safety, interrelating the many antiarrhythmic agents.[4] Comparative studies with quinidine have formed an important part of the development program for moricizine.

METHODS

Study design (Fig. 5): Study EN/313-N-46 compared the efficacy and safety of moricizine with quinidine sulfate in a 7-week study with a randomized, double-blind, placebo-controlled crossover design.[5] The crossover phase consisted of 5 periods: periods 1, 3 and 5 were 1-week placebo-dosing intervals, and periods 2 and 4 were 2-week active drug treatment phases in which patients received moricizine and quinidine in randomized order. A

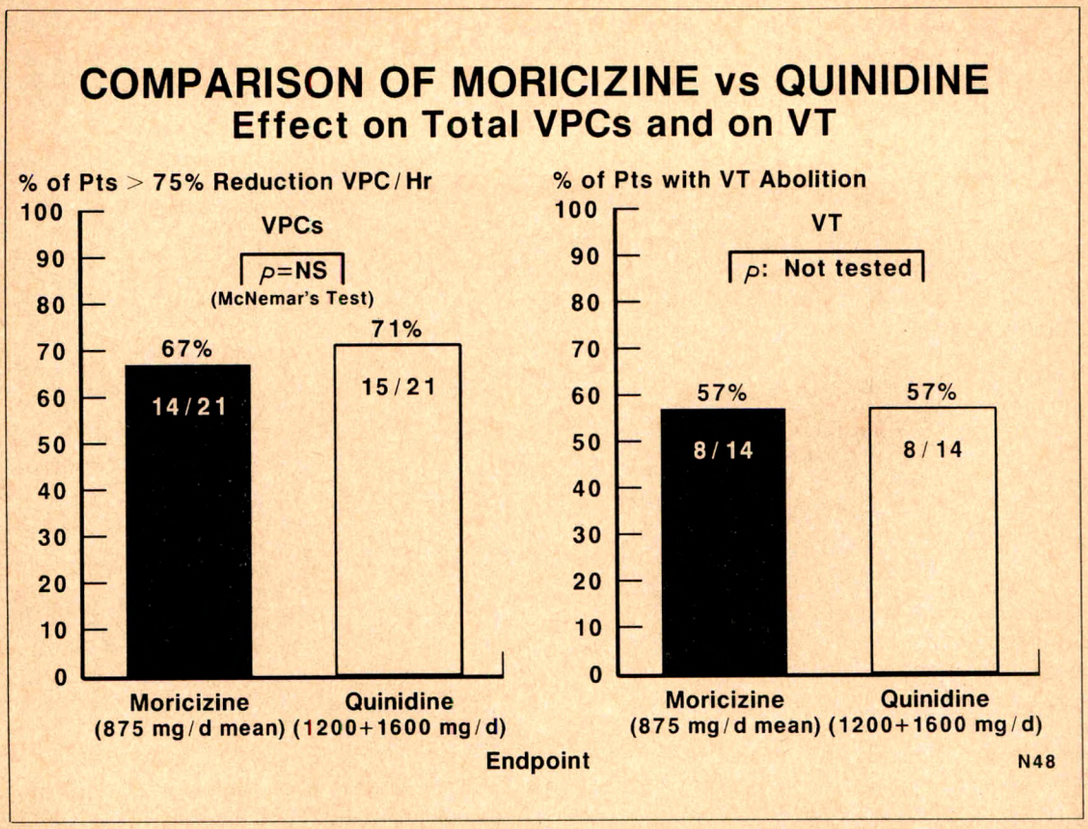


FIGURE 6. Response of ventricular premature complexes (VPCs) to therapy with moricizine vs quinidine. Abbreviations as in Figures 1 and 2.

4-year, open-label moricizine extension phase followed the controlled trial.

Study medications: Moricizine was administered daily in 3 equally divided doses based on body weight (10 to 12 mg/kg/day). Permissible dosage range was 600 to 1,200 mg/day, with an intended average of about 900 mg/day (actual mean 875 mg/day). Quinidine was administered as the sulfate salt, given in 4 equally divided doses at 1,200 mg/day during the first week, and an adjusted dosage (based on tolerance) of 1,200 mg/day (n = 17) or 1,600 mg/day (n = 5) during the second week.

Study group: Thirty-five patients entered the moricizine-quinidine comparative trial (24 men and 11 women, average age 55.7 years, range 24 to 70). Arrhythmias were classified as symptomatic or prognostically important, or both; only 3 were in the benign risk category. Nearly one-half of the patients (16 of 35) had received prior antiarrhythmic agents (mean 2.8, range 1 to 6). Associated cardiovascular diagnoses were present in 33 patients and included hypertension in 49% and chronic ischemic heart disease in 46%. Of 35 entering patients, 30 completed the crossover phase, 4 were withdrawn for insufficient arrhythmia or personal reasons, and 1 because of an adverse drug reaction. Twelve patients entered the extension phase and 5 were ongoing at a duration of dosing of 113 to 917 days.

RESULTS (FIG. 6)

Efficacy: Moricizine (mean 875 mg/day) and quinidine (mean 1,300 mg/day) were equally effective in ventricular arrhythmia suppression. Geometric mean percent reduction in VPCs per hour during week 1 was 96% during moricizine and 92% during quinidine therapy; during week 2 (end point analysis) it was 95% during moricizine and (identically) 95% during quinidine therapy. Of 21 patients with paired, analyzable data for all treatment periods during the crossover phase, 67% responded to moricizine (≥75% reduction of total VPCs per hour) and 71% to quinidine at the end point.

Treatment of nonsustained VT was reduced by an identical 90% rate with each drug, and VT abolition was achieved in 57% of patients in each group. Ten patients had analyzable data in the extension phase. Moricizine was consistently efficacious in all but 1 patient for up to 36 months of follow-up.

Safety: During the crossover phase, at least 1 adverse experience was reported in 21 patients taking quinidine, 18 taking moricizine and 5 taking placebo. Of 30 patients completing the crossover phase, 7 subsequently discontinued quinidine, 3 moricizine, and 3 both drugs because of adverse effects. (Two additional, noncompleting patients also discontinued therapy for adverse reactions, 1 taking each drug.) Dizziness, gastrointestinal disturbance and fatigue were the most frequent subjective complaints with

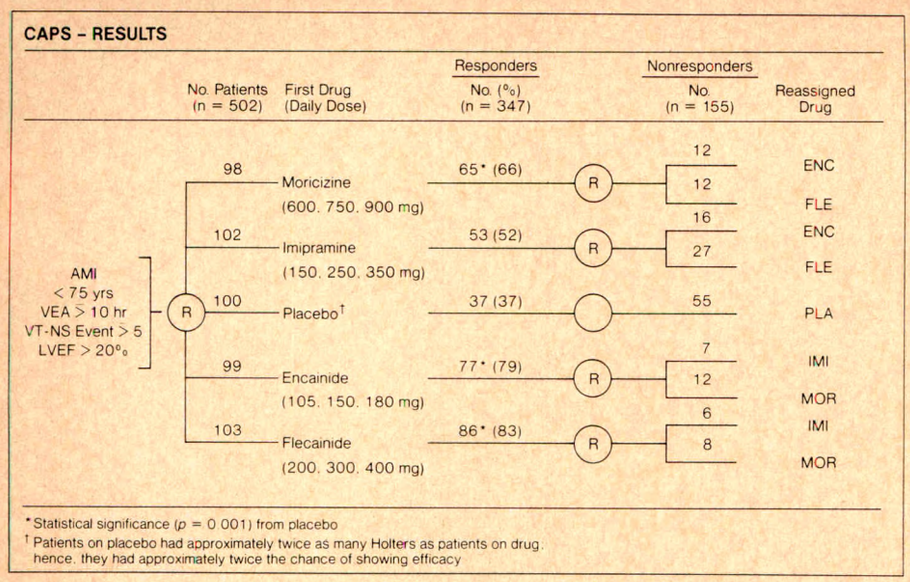


FIGURE 7. Randomization scheme and initial patient outcome in the Cardiac Arrhythmia Pilot Study (CAPS). AMI = acute myocardial infarction; ENC = encainide; FLE = flecainide; IMI = imipramine; LVEF = left ventricular ejection fraction; MOR- = moricizine; PLA = placebo; other abbreviations as in Figures 1 and 2.

moricizine, and gastrointestinal disturbance and fatigue were the most common complaints with quinidine. Significant differences in adverse-effect profile included dizziness with moricizine and diarrhea with quinidine. Mild hepatitis was induced by quinidine in 1 patient. New rhythm disturbances included left bundle branch block with moricizine and junctional escape rhythm with quinidine. Moricizine caused increases in ventricular depolarization (QRS interval prolongation) and quinidine caused increases in ventricular repolarization (QT interval). During the extension phase, 2 patients discontinued taking moricizine because of drug-related adverse reactions.

Other comparisons: In an earlier comparison (study N10) of moricizine in lower doses (600 to 900 mg/day) and quinidine in higher doses (1,600 mg/day), a good but somewhat lower VPC response and comparative efficacy rate was observed with moricizine: geometric mean percent VPC reduction was 68% for moricizine (n = 23) and 89% for quinidine therapy (n = 24).[8]

Conclusion: These data indicate that moricizine in higher dosages (mean 900 mg/day) achieves efficacy comparable to that of quinidine, titrated to tolerance (1,300 mg/day), in reducing ventricular arrhythmias but shows a different adverse effect profile, including fewer reactions requiring drug discontinuation.

CAPS

CAPS[6,7] and the ongoing Cardiac Arrhythmia Suppression Trial (CAST) form crucial tests of antiarrhythmic drug efficacy and safety in postmyocardial infarction patients with prognostically important ventricular arrhythmias. In CAPS, 4 active agents and placebo were selected for testing among the approved and available investigational agents in 1983 that were judged to show the most promise for achieving and maintaining arrhythmia suppression and drug tolerance in 70% or more of patients during initial testing and long-term therapy (at least 1 year). The 4 agents selected by the multicenter CAPS investigators included moricizine, encainide, flecainide and imipramine. Standard agents were considered, but believed to have already been sufficiently tested to indicate an inadequately promising benefit/risk ratio. The specific purpose of CAPS was to determine the feasibility of conducting a full-scale trial to test the hypothesis that survival is improved by long-term suppression of ventricular arrhythmias after acute myocardial infarction. An important objective of CAPS was to determine the extent to which the specific drug regimen selected could successfully suppress ventricular arrhythmias.

METHODS

Study design and patient selection: CAPS was a double-blind, placebo-controlled, randomized trial conducted at 10 clinical centers in the United States and Canada. The trial was divided into 3 main phases, including (1) patient recruitment, (2) drug/dose selection, and (3) 1 year follow-up.

Patients were eligible if they had a documented acute myocardial infarction within 6 to 60 days of enrollment, were younger than age 76 years, demonstrated ≥10 VPCs/hour or ≥5 episodes of nonsustained (<10 beats) VT on a qualifying 24-hour ambulatory electrocardiogram (Holter), and had a left ventricular ejection fraction of ≥20%.

Qualifying patients were assigned to therapy with 1 of the 4 active treatment drugs or placebo (Fig. 7). Drugs and placebo were titrated up to 3 doses to achieve the suppression goal of ≥70% reduction in VPCs and ≥90 to 100% reduction in nonsustained VT events without intolerable side effects. If titration in the CAPS drug no. 1 resulted in intolerance or inefficacy, rerandomization to a second drug occurred. Patients who began therapy with class IC drugs (encainide or flecainide) were crossed over to non-IC drugs (moricizine or imipramine) and vice versa. Placebo patients were reassigned to placebo. When an effective or preferred drug and dose were found, patients entered a 1-year follow-up phase, during which 24-

TABLE I Results of the Cardiac Arrhythmia Pilot Study

	Initial Phase (Dose-Finding)				Follow-Up Phase (to 1 Year)			
			Intolerable Effects (% Pts.)				Withdrawals (% Pts.)[§]	
Drug*	No. of Pts.	Efficacy (% Pts.)	Proarrhythmia	Other	No. of Pts.[†]	Efficacy (% Pts.)[‡]	Adverse Effects	Misc.
Encainide	99	79	1	9	85	76	21	7
Flecainide	103	83	3	12	86	77	26	4
Imipramine	102	52	1	31	54	54	52	17
Moricizine	98	66	1	9	65	61	34	9
Placebo	100	37	3	11	46	30	37	15

* Initially assigned drug (drug 1).
† Number of patients taking drug 1 at end of dosing.
‡ Efficacy of drug 1 (average over first year).
§ Number of patients withdrawn compared with number of patients taking drug 1 at end of dosing.
Misc. = miscellaneous.

hour Holter recordings and clinic visits were performed at 3, 6, 9 and 12 months, during continued blinded therapy.

Study population: Of 10,734 screened, age-eligible patients with myocardial infarction, 502 qualified, consented and were randomized to CAPS therapy. Most of the patients (83%) were men (average age 59 ± 9 years, range 21 to 74). Thirty-four percent had nonsustained VT on baseline Holter monitoring, and 35% had substantial depression in left ventricular function (ejection fraction <0.40). Baseline patient characteristics were distributed remarkably evenly across the 5 initial CAPS randomization groups.[7]

Drug dosage: All drugs were administered in divided doses 3 times daily. For moricizine, daily doses were 600, 750 and 900 mg/day. For flecainide, doses were 200, 300 and 400 mg/day. Encainide doses were 105, 150 and 180 mg/day. Imipramine was given in doses of 150, 225 and 375 mg/day.

RESULTS

Initial response in number (%) of patients meeting CAPS efficacy criteria by drug-1 assignment is listed in Table I and Figure 7.[6] In addition, geometric mean reduction in rates of total VPCs at the end of titration are given. The response rate of moricizine was intermediate between that of imipramine and placebo (the least effective drug) and that of encainide and flecainide (class IC agents). Reductions in nonsustained VT events by active therapy, particularly with moricizine, flecainide and encainide, compared with placebo, were particularly impressive (>90 vs 70%) ($p < 0.01$). Patients with a prior history of heart failure or an ejection fraction of <0.40 responded to moricizine as well as or better than patients did to encainide/flecainide.

During the long-term follow-up phase, responses paralleled those of initial therapy, with approximately 5 to 10% reductions from initial rates in all groups (Table I).

Safety: Of entered patients, 431 (86%) completed the 1-year trial and 71 (14%) terminated prematurely because of refusal to continue in 27, loss to follow-up in 4, and death in 40. In addition, 168 patients (33%) discontinued their assigned CAPS drug before study completion because of adverse effects, disqualifying VT or proarrhythmia, or patient refusal. Overall, adverse effects were reported no more frequently with moricizine than with placebo, both short- and long-term. Flecainide and encainide were also well tolerated, in contrast to imipramine. During short-term dosing, however, slightly more patients taking moricizine than placebo reported dizziness (37 vs 29%), nausea (13 vs 7%) and fever (6 vs 2%). During long-term follow-up, fatigue, dizziness and nausea were reported with slightly greater (2 to 10%) frequency with the drug than with placebo. The study was not designed as a mortality trial, and these events were far too infrequent to establish even reasonable trends with respect to potential mortality benefits or risks of the individual therapy arms. Rates of monitor-defined proarrhythmia were low, both in absolute terms and compared with placebo, in all active treatment arms. The risk of developing new or increased heart failure was greatest during therapy with flecainide and similar to or less than therapy with placebo on the other drugs, including moricizine.

Conclusions: CAPS demonstrated the feasibility of recruiting and successfully treating patients with myocardial infarction with 3 of the active treatment arms tested (moricizine, encainide and flecainide). Short-term efficacy with moricizine was substantially greater than that with placebo, both in percent of patients reaching previously defined levels of suppression and geometric mean VPC and nonsustained VT reductions. Long-term (1 year) evaluations documented significantly greater antiarrhythmic activity in moricizine- than in placebo-treated patients. CAPS also provided the reassuring result that the sum of serious adverse events (death/cardiac arrest, proarrhythmia, sustained VT, congestive heart failure) occurred less often during moricizine than during placebo therapy. Compared with placebo, mean PR and QRS intervals in this population were slightly prolonged during moricizine therapy, but mean QTc interval shortened slightly.

CAST

Based on their favorable efficacy/tolerance performance in CAPS, moricizine, flecainide and encainide were chosen for evaluation in CAST.[9] Although this trial is still ongoing, 2 important results are already apparent. First, despite high rates of VPC suppression and good

tolerance (with respect to noncardiac adverse effects), the class IC agents encainide and flecainide increased risk (by 2.5-fold for total death or cardiac arrest, and 3.6-fold for arrhythmic deaths/cardiac arrest). On April 17, 1989, the CAST data and safety monitoring board recommended (1) discontinuation of the arms with class IC antiarrhythmic action (encainide/flecainide), and (2) continuing therapy in the moricizine arm, which did not share this adverse trend. Data for moricizine remain blinded; however, it was stated that no significant difference was present (in either direction) with respect to moricizine vs placebo mortality. These results emphasize the need to evaluate each antiarrhythmic drug and drug class separately for effects on mortality in the postinfarct population. Because of its position in CAST, moricizine is the only other class I antiarrhythmic agent for which mortality results will be available in the near future (and the only one for which a beneficial effect may possibly be shown).

CONCLUSIONS

These comparative trials indicate that moricizine is a promising new antiarrhythmic agent when profiled against other drugs frequently used for therapy of chronic ventricular arrhythmias. In efficacy, moricizine is superior to β-blocking therapy (propranolol) and to some class I agents (i.e., disopyramide) and is equivalent to quinidine. Although moricizine is somewhat less effective in a dosage of 600 to 750 mg/day than the class IC agents encainide and flecainide, these class IC drugs are now known to increase risk in postinfarction patients.[9] Moricizine is also a well-tolerated antiarrhythmic agent. Therapy with moricizine is associated with fewer discontinuations than with propranolol, disopyramide and quinidine. Whether a favorable mortality effect can be achieved by therapy with moricizine (or any other class I agent) in patients with prognostically important ventricular arrhythmias is unknown but is being tested. However, the potential for adverse mortality effects, recently shown for encainide/flecainide, has not been suggested for moricizine. This favorable profile makes moricizine an agent of unique interest.

REFERENCES

1. Butman SM, Knoll ML, Gordin JM. Comparison of ethmozine to propranolol and the combination for ventricular arrhythmias. *Am J Cardiol 1987;60:603–607.*

2. Pratt CM, Young JB, Francis MJ, Taylor AA, Morton HJ, English L, Mann DE, Kopelen H, Quinones MA, Roberts R. Comparative effect of disopyramide and ethmozine in suppressing complex ventricular arrhythmias by use of a double-blind, placebo-controlled, longitudinal crossover design. *Circulation 1984;69:288–297.*

3. Pratt CM, Butman SM, Young JB, Knoll M, English L. Antiarrhythmic efficacy of ethmozine (moricizine HCl) compared with disopyramide and propranolol. *Am J Cardiol 1987;60:52F–58F.*

4. Anderson JL. Criteria for selection of oral drug therapy in chronic ventricular arrhythmia. *Mod Med 1987;55:48–66.*

5. Kennedy HL, DeMaria AN, Sprague MK, Weene RD, Reed RM, Janosik DL, Buckingham TA. Comparative efficacy of moricizine and quinidine for benign and potentially lethal ventricular arrhythmia. *Am J Noninvasive Cardiol 1988;2:98–105.*

6. The Cardiac Arrhythmia Pilot Study (CAPS) Investigators. Effects of encainide, flecainide, imipramine and moricizine on ventricular arrhythmias during the year after myocardial infarction: the CAPS. *Am J Cardiol 1988;61:501–509.*

7. The Cardiac Arrhythmia Pilot Study (CAPS) Investigators. Recruitment and baseline description of patients in the cardiac arrhythmia pilot study. *Am J Cardiol 1988;61:704–713.*

8. Morganroth J, Orth DW, Dunkman WB, Pearlman AS, Horowitz LN, Josephson ME, Kastor JA. Comparative antiarrhythmic efficacy and tolerance of ethmozine and quinidine. *Circulation 1978;II-103:57–58.*

9. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med 1989;321:406–412.*

Efficacy of Moricizine in Malignant Ventricular Arrhythmias

Leonard N. Horowitz, MD

Moricizine hydrochloride has been shown to be effective in the treatment of a variety of ventricular arrhythmias. It has been evaluated for the treatment of malignant ventricular arrhythmias in several hundred patients. When assessed by noninvasive techniques, moricizine effectively suppresses spontaneous unsustained ventricular tachycardia (VT) in approximately 60% of patients. Efficacy is sustained during long-term therapy. Evaluation of moricizine therapy for sustained VT using programmed stimulation has been carefully performed in more than 100 patients. The initiation of sustained VT is suppressed in 20 to 25% of patients. Moricizine is generally well tolerated. Because of its minimal effects on left ventricular function, a common clinical problem in patients with malignant ventricular arrhythmias and relatively low potential for proarrhythmia, moricizine has a role in the treatment of malignant ventricular arrhythmias in selected patients.

(Am J Cardiol 1990;65:41D–46D)

From the Philadelphia Heart Institute, Presbyterian Medical Center of Philadelphia, Philadelphia, Pennsylvania.

Address for reprints: Leonard N. Horowitz, MD, Philadelphia Heart Institute, Presbyterian Medical Center of Philadelphia, 39th and Market Streets, Philadelphia, Pennsylvania 19104.

Moricizine hydrochloride has been shown to be effective in the treatment of various forms of ventricular ectopic activity. Because it has an acceptable side-effect profile, a low incidence of proarrhythmia, and modest effects on left ventricular (LV) function and intraventricular conduction, it appears well suited for treatment of patients with malignant ventricular arrhythmia.[1,2] These patients frequently have LV dysfunction and atrioventricular (AV) conduction disturbances which may limit the use of certain antiarrhythmic drugs. The present review was undertaken to evaluate the efficacy of moricizine in patients with malignant ventricular arrhythmias.

METHODS

The moricizine data base containing information on patients with malignant ventricular arrhythmias treated with moricizine was reviewed and pertinent data were extracted and presented in this review.[3,4] The patient population, study design, results and statistical analyses are presented in this report. In addition, a review of published reports was performed and pertinent publications are incorported into this report.

DEFINITIONS

Malignant (lethal) ventricular arrhythmias were considered sustained ventricular tachycardia (VT) (≥15 complexes of VT), ventricular flutter and ventricular fibrillation. Potentially malignant (lethal) ventricular arrhythmias were symptomatic unsustained VT associated with significant structural heart disease. In patients with these latter symptoms, LV dysfunction was typically present.

The efficacy of moricizine therapy was assessed by either noninvasive or invasive techniques. Noninvasive evaluation included 24-hour Holter monitoring or exercise stress testing, or both. The criteria for efficacy of Holter monitoring was a ≥75% reduction in the frequency of ventricular premature complexes (VPCs) and elimination of sustained VT when the Holter monitor recorded during moricizine administration was compared with the baseline recording. The criteria for efficacy during exercise testing was ≥50% reduction in VPCs, ≥90% reduction of couplets and elimination of VT.

The efficiency of moricizine therapy was evaluated with invasive techniques using standard electrophysiologic techniques and programmed electrical stimulation. The response to programmed stimulation during moricizine administration was compared with the baseline study. Noninducible VT was defined as initiation of <15

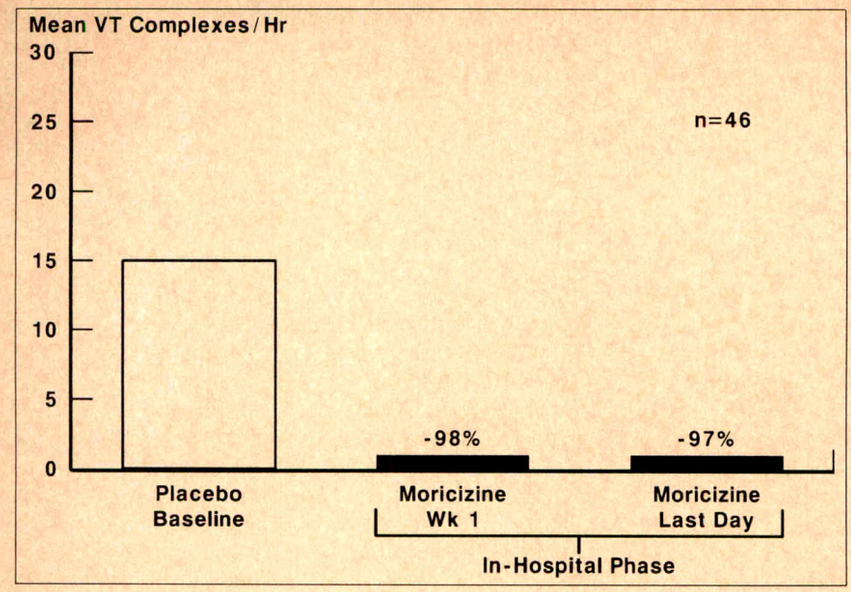


FIGURE 1. Noninvasive evaluation of moricizine in patients with life-threatening ventricular arrhythmias. Mean number of ventricular tachycardia (VT) complexes per hour are shown on the *ordinate*. *Columns* from *left* to *right* represent the baseline Holter monitor recording results during the placebo phase and the Holter monitor results at the end of the first week of moricizine therapy; the *last column* represents the results of the last in-hospital day monitoring during moricizine therapy. Note that significant suppression of VT occurred during both monitoring sessions of the in-hospital phase.

complexes of VT during moricizine therapy. If the VT was initiated by 1 or 2 extrastimuli during the baseline study, the VT was considered noninducible if <15 complexes were induced by 1 and 2 extrastimuli. If sustained VT was initiated by 3 extrastimuli, the arrhythmia was considered noninducible. If VT induction required 3 extrastimuli at baseline, a noninducible response with moricizine required that <15 complexes of VT were induced with at least 3 extrastimuli. Initiation of a slower but still sustained VT was not considered a partial response in this analysis.

NONINVASIVE EVALUATION OF PATIENTS WITH LIFE-THREATENING VENTRICULAR ARRHYTHMIAS

In patients with life-threatening ventricular arrhythmias, the long-term safety and efficacy of moricizine assessed by noninvasive monitoring was studied. Forty-six patients were enrolled in this study. Malignant arrhythmias were present in 18 patients and potentially malignant arrhythmias were present in 28. The arrhythmias had proved refractory to 1 to 6 previous trials of antiarrhythmic therapy. Congestive heart failure was present in 67% of the patients. LV ejection fractions ranged from 0.12 to 0.70 (mean 0.36). Seventy-four percent of the patients had an ejection fraction ≥0.30. After a placebo period, the patients received moricizine in a daily dose of 600 to 1,500 mg/day. The mean dose was 822 mg/day (mean 10.4 mg/kg/day).

The primary efficacy analysis in this study was based on the suppression of unsustained VT when comparing baseline with recordings during treatment. Efficacy was noted in 27 of 45 patients (60%). No change was noted in 16 patients (36%) and the arrhythmia worsened in 2 patients (4%). The change from baseline was statistically significant ($p < 0.01$). Improvement was noted in 43% of patients with unsustained VT at baseline and in 93% of patients with sustained VT.

Ambient ventricular arrhythmias were significantly reduced during the in-hospital phase of this study (Fig. 1). The mean VT complexes per hour were reduced by 97 to 98%, and the number of VT events was reduced by 96%. The mean total VPC frequency was also significantly reduced (94%). During the inpatient phase of this study, 30 of 46 patients (65%) had a ≥75% reduction in total VPC frequency.

The suppression of ambient ventricular ectopy was maintained during the 1-year follow-up of this study (Fig. 2). Significant VPC, ventricular couplet and VT suppression (94, 99 and 99%, respectively) were observed.

During this study, 42 of 48 patients reported at least 1 adverse experience. Most were minor and included dizziness, headache and nausea. In 4 patients, moricizine was discontinued because of proarrhythmia and 1 death was attributable to proarrhythmia. The 7 additional deaths in this study were not attributed to moricizine therapy. There was no evidence of worsening of heart failure in the study.

Electrocardiographic changes were not infrequent. Thirteen of 48 patients (27%) had first-degree AV block during moricizine administration. Left bundle branch block developed in 3 patients during the study.

During the inpatient phase of this study, 15 patients discontinued therapy. In 6 this was due to lack of efficacy, in 3 proarrhythmia, in 2 death, and in 4 other causes were present. In the outpatient phase, 15 of 33 patients (45%) discontinued moricizine therapy. Discontinuation was due to loss of efficacy in 3, adverse reactions in 6, arrhythmic death in 2 and nonarrhythmic death in 3.

MORICIZINE COMPASSIONATE-USE STUDY

The moricizine compassionate-use study in patients with life-threatening arrhythmias was a multicenter, open-label study to evaluate moricizine in patients with life-threatening ventricular arrhythmias in whom marketed antiarrhythmic agents had been ineffective, not tolerated or contraindicated. An in-hospital initiation and titration phase was followed by a long-term outpatient

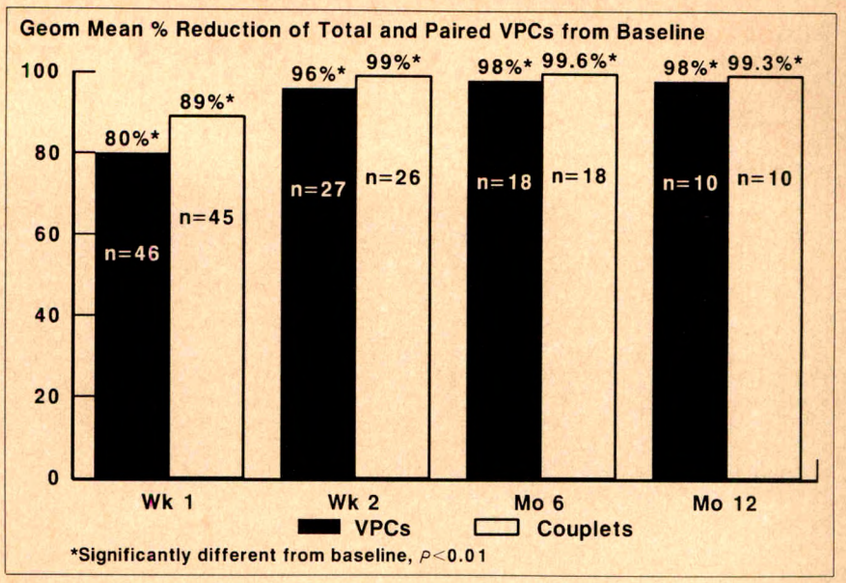


FIGURE 2. Noninvasive evaluation of moricizine in patients with life-threatening ventricular arrhythmias. This graph depicts the results of moricizine therapy in suppression of ventricular premature complexes (VPCs) and ventricular couplets. Mean percent reduction of VPCs and ventricular couplets from the baseline Holter monitoring session are shown on the *ordinate*. Results at 1 week, 2 weeks, 6 months and 12 months of moricizine therapy in patients with life-threatening ventricular arrhythmia are shown on the *abscissa*. Geom = geometric.

treatment phase in initial responders. In this study, efficacy criteria were determined by individual investigators. In addition, a global assessment of each patient was requested of the investigator.

There were 263 patients enrolled in this study. Malignant ventricular arrhythmias were present in 187 of 263 (71%) and potentially malignant arrhythmias were present in 75 of 263 patients (29%). Coronary artery disease was present in 201 of 263 patients (76%), and congestive heart failure was present in 159 of 263 patients (50%). Symptoms related to arrhythmias were present in 224 of 263 patients (85%). Cardioversion had been required in 123 of 263 patients, almost 50%.

Patients were administered moricizine on a per kg body weight basis. The average dose of moricizine in this study was 11.0 mg/kg/day.

In this study, the efficacy of moricizine was defined as a clinically significant reduction in the frequency of the ventricular arrhythmia. A global assessment of efficacy could not be performed in 9 patients because of adverse reactions or death early in the in-hospital treatment phase. In the remaining patients, moricizine was effective in 121 of 254 (48%) patients. A positive global evaluation was seen more often in patients with potentially malignant arrhythmias than in patients with malignant arrhythmias (Fig. 3). In this study, 49% of patients with sustained VT were judged to have responded to moricizine therapy. The global response was positive in 59% of patients with sustained VT.

There was no statistically significant correlation between the global response to moricizine therapy and the moricizine dose or demographic factors. Patients who had previously responded to procainamide or propafenone, however, responded more frequently to moricizine therapy.

As in the previous study, moricizine significantly reduced the frequency of VPCs, ventricular couplets, and runs and total complexes of unsustained VT in a small

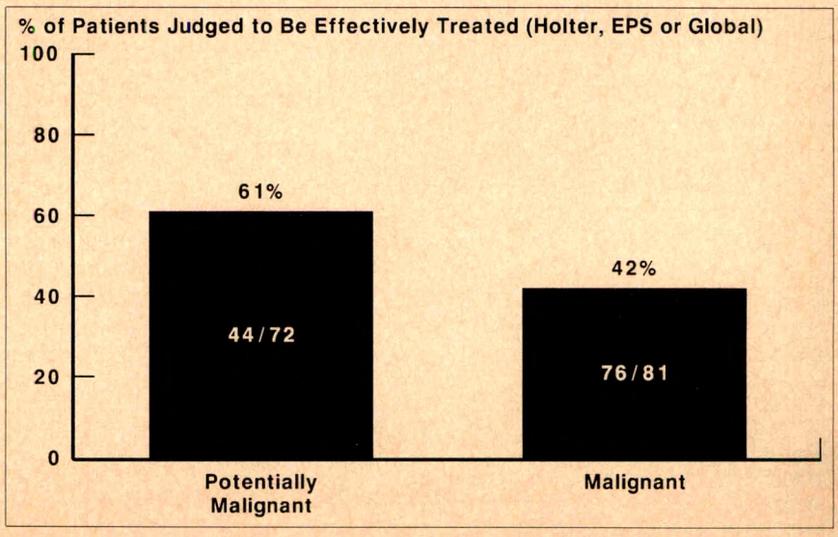


FIGURE 3. Moricizine efficacy stratified by the type of ventricular arrhythmia treated. Percentage of patients judged to be effectively treated by either Holter monitoring, electrophysiologic study (EPS) or global assessment of the investigator is shown on the *ordinate*. *Columns* on the *abscissa* represent patients who at baseline had potentially malignant ventricular arrhythmia (*left*) and malignant ventricular arrhythmia (*right*).

TABLE I Characteristics of Patients with Paired PES Studies Treated with Morcizine

No. of pts	117
Age (yrs)	59.8 ± 11.0
Range (yrs)	(25–79)
Gender (men)	99 (85%)
Coronary artery disease	93 (79%)
Prior myocardial infarction	80 (68%)
Congestive heart failure	77 (66%)
Controlled studies	67 (57%)
Compassionate-use	50 (433%)
Arrhythmia-induced at first study	
Sustained VT	75 (64%)
Unsustained VT	34 (29%)
Other	8 (7%)
Syncope	38 (32%)
Cardiac arrest	34 (29%)
Previous cardioversion	88 (75%)
LV ejection fraction (mean)	33.6 ± 16.5 (n = 31)
0.30	13 (42%)
0.30–0.45	11 (36%)
>0.45	7 (23%)

LV = left ventricular; PES = programmed electrical stimulation; VT = ventricular tachycardia.

subset of patients who had paired Holter recordings or had undergone exercise testing, or both. Statistically significant reductions were observed between week 1 and year 1 of the study. VT was completely suppressed in 42 to 71% of patients at various sampling intervals. Reduction in VT frequency of a similar magnitude was observed during paired exercise tests.

Adverse drug reactions, possibly, probably or definitely related to moricizine, were reported in 87 of 263 patients (33%). Most frequently, nausea and dizziness were reported. Moricizine was discontinued in 49 of 263 patients (19%) because of adverse experiences. A pattern of clinically significant abnormal laboratory results were not observed during this study.

A modest number of significant electrocardiographic abnormalities were noted in the study. Three patients developed AV conduction disturbances, 3 developed intraventricular conduction disturbances and 1 patient developed sinus node dysfunction. Increases in the PR interval were frequently noted in this study. In 67% of patients, the PR interval increased and in 26% of patients with a normal baseline interval, first-degree AV block was noted during moricizine therapy. The mean increase in PR interval, however, was 25 ms. The mean change in QRS interval duration was 12 ms. Although this was statistically significant, it had no clinical importance. Repolarization was not significantly effected by moricizine.

TABLE II Relation of Morcizine Dose and Response by Programmed Stimulation Among 117 Patients with Paired Studies

Dose (mg/Day)*	Responders (n = 34)	Nonresponders (n = 83)	Percent Response
All Patients			
<525	1 (3%)	---	–%
600	2 (6%)	7 (8%)	22%
750	5 (15%)	19 (23%)	21%
900	11 (32%)	32 (39%)	26%
1,050	6 (18%)	12 (15%)	33%
1,200	4 (12%)	10 (12%)	29%
≥1,275	5 (15%)	3 (4%)	63%
	34 (100%)	83 (100%)	29%
Chi-square for equal proportions = 0.23			
Patients with Sustained Ventricular Tachycardia at Baseline			
<525	1 (5.3%)	0	100%
600	2 (11%)	4 (7.1%)	33%
750	1 (5.3%)	15 (27%)	7%
900	6 (32%)	24 (43%)	20%
1,050	5 (26%)	8 (14%)	39%
1,200	2 (11%)	4 (7.1%)	33%
≥1,275	2 (11%)	1 (1.8%)	66%
	19 (100%)	56 (100%)	25%
Chi-square for equal proportions = 0.10			

* Dose categories: 600 = 525 to 674 mg/day; 750 = 675 to 824 mg/day; 900 = 825 to 974 mg/day; 1,050 = 975 to 1,124 mg/day; 1,200 = 1,124 to 1,274 mg/day.

EVALUATION OF MORICIZINE THERAPY BY PROGRAMMED ELECTRICAL STIMULATION

In 8 individual studies and the compassionate-use study of moricizine, a total of 117 patients underwent paired programmed electrical stimulation tests which included a baseline (without the drug) study and a study with moricizine. The patients enrolled in these studies were typical of patients with sustained VT who undergo electrophysiologic testing. Most of the patients had sustained VT (53%) or ventricular fibrillation (29%), and conventional antiarrhythmic agents were contraindicated, ineffective or not tolerated. Most of the patients were men, and coronary artery disease and prior myocardial infarction were the most common forms of heart disease. LV dysfunction, assessed by LV ejection fraction and the presence of congestive heart failure, was typical (Table I). All patients had previously been treated with antiarrhythmic agents and a mean of 4.7 drugs had been administered to this group of patients.

The arrhythmia induced at the first electrophysiologic study was sustained VT in 75 patients (64%). Other sustained arrhythmias were induced in 8 patients (7%). Unsustained VT was initiated by programmed stimulation in 34 patients (29%).

Patients were given moricizine at a mean daily dose of 936 mg at the time of the electrophysiologic study. Therapy had been administered for a mean of 6 days before the electrophysiologic test.

Sustained VT could no longer be initiated by programmed electrical stimulation in 19 of 75 patients (25%) while taking moricizine. Other sustained arrhythmias and unsustained VT were no longer inducible in 15 of 42 patients (36%) whose arrhythmias were initiated at the baseline study. Overall, 29% of patients responded to moricizine.

Paired electrophysiologic data were not available for 45 additional patients who underwent a baseline electrophysiologic study. These patients did not undergo a second study for a variety of reasons, most often a lack of efficacy judged by noninvasive techniques (20 patients), proarrhythmia (7 patients) and drug adverse effects (4

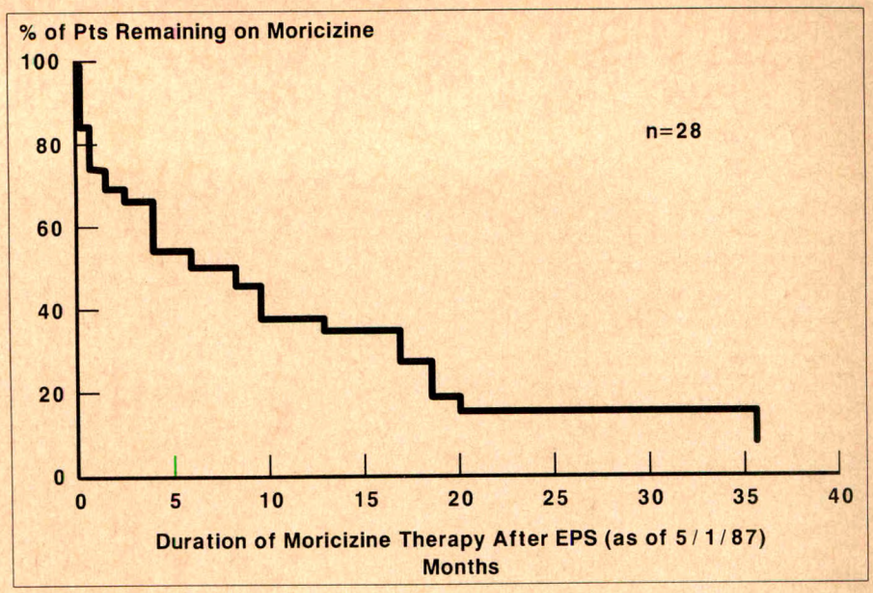


FIGURE 4. Results of chronic treatment with moricizine in patients who responded during electrophysiologic evaluation. This graph shows the duration of moricizine therapy after electrophysiologic evaluation in patients in whom previously inducible ventricular tachycardia was suppressed by moricizine therapy. Percentage of patients continuing to take moricizine is shown on the *ordinate* and the time shown in months is seen on the *abscissa*. EPS = electrophysiologic study.

patients). If using an intention-to-treat analysis, these patients were included in the overall efficacy calculation. Patients with sustained VT at baseline had a 21% (19 of 91) response rate to moricizine.

Moricizine therapy was continued after the electrophysiologic study in 28 of the 34 responders. Six received alternative therapy at the discretion of the investigator.

The daily moricizine dose ranged from 450 to 1,500 mg. Whereas the mean dose for the study group was 936 mg/day, the range was wide and an analysis was undertaken to determine whether there was a relation between moricizine dose and antiarrhythmic response as judged by programmed electrical stimulation. There was no apparent relation between the moricizine dose and the outcome of electrophysiologic testing (Table II).

In the 28 responders treated with moricizine for 3 to 1,530 days (mean 203), the cumulative percentage of patients remaining who continued to take moricizine after hospital discharge is shown in Figure 4. Therapy was discontinued in 2 patients because it was no longer required and in 6 patients because of loss of efficacy. There were 3 sudden cardiac deaths and 2 deaths due to congestive heart failure during the follow-up period. In 6 patients, adverse drug reactions caused drug discontinuation and in 2 patients, a non–drug-related adverse event prompted drug discontinuation.

In 13 patients who did not respond to moricizine by electrophysiologic criteria, moricizine was continued during the follow-up period. Five of these patients died, 3 suddenly, and only 3 continued long-term therapy.

DISCUSSION

Review of the moricizine data base shows that in patients with sustained VT evaluated by programmed electrical stimulation, the arrhythmia was suppressed by moricizine in 20 to 25%. This is in agreement with reported results from several centers in which efficacy rates of 10 to 30% have been reported.[5–10] This efficacy was achieved at doses comparable to those reported from the moricizine data base. In addition, other electrophysiologic effects noted in most studies were an increase in the HV interval and the QRS duration. Approximately 50% of the studies showed a change in the AH interval indicating depression of AV nodal function; however, this was not a uniform finding.[5–10]

In patients in whom sustained VT remained inducible, moricizine generally produced an increase in the VT cycle length (a slowing in VT rate). The magnitude of the change ranged from 13 to 30%; however, most studies showed a 13 to 17% increase.[5–10] These changes are similar to those produced by procainamide, quinidine and mexiletine. They are, however, less than the changes produced by amiodarone, flecainide, or quinidine/mexiletine combination which produce 25, 60 and 40% reductions, respectively.[11–13]

The moricizine data base reveals a significant incidence of drug discontinuation during follow-up. The reasons for this are varied but there is a significant incidence (approximately 15%) of loss of efficacy. The causes for this have not been well studied and progression of underlying disease may play a role.

Studies to date have generally been performed in patients with refractory arrhythmia and the results in patients with fewer previous drug failures are unknown. The present review is limited by the lack of prospective studies of patients with malignant arrhythmia treated with moricizine. The current data were collected over the past decade with little uniformity in protocols, definitions, criteria of efficacy or proarrhythmia. Moreover, the number of patients with malignant arrhythmia who were treated for longer periods of time with moricizine is relatively small. Although chronic moricizine therapy has generally been well tolerated, this small number of patients treated for longer periods of time is a considerable limitation of this review.

In these studies, the potentiation of congestive heart

failure and conduction of proarrhythmia by moricizine has been minimal. The patients included in these studies have generally been typical of patients with malignant arrhythmias, namely, with a high incidence of congestive heart failure, LV dysfunction and severe heart disease, and thus this relatively low incidence of severe adverse effects is promising. Compared with drugs in other classes (IA, IC and III), the reported incidence of these serious cardiac adverse effects is low. Comparative trials, however, are needed before definitive conclusions about the relative safety of moricizine can be made.

Based on limited data available, it appears that moricizine is an effective drug for control of malignant ventricular arrhythmias in selected patients. Its potential for proarrhythmia and worsening of congestive heart failure is relatively low and its efficacy appears to be comparable to other frequently used antiarrhythmic agents.

REFERENCES

1. Smetnev AS, Shugushev KK, Rosenshtraukh LV. Clinical electrophysiologic and antiarrhythmic efficacy of moricizine HCl. *Am J Cardiol 1987;60:40F–47F.*

2. The Cardiac Arrhythmia Pilot Study (CAPS) Investigators. Effects of encainide, flecainide, imipramine and moricizine on ventricular arrhythmias during the year after acute myocardial infarction: the CAPS. *Am J Cardiol 1988;61:501–509.*

3. Ethmozine (Morcizine HCl) NDA Submission. *E.I. Du Pont de Nemours & Co., Wilmington, 1987.*

4. Ethmozine (Morcizine HCl) NDA Presentation. *FDA Cardio-Renal Advisory Committee Meeting, January 27, 1989.*

5. Doherty JU, Rogers DP, Waxman HL, Buxton AE. Electrophysiologic properties and efficacy of ethmozine in sustained ventricular tachycardia (abstr). *Circulation 1984;70:II:II-440.*

6. Mann DE, Luck JC, Pratt CM, Magro SA, Sakun V, Katz SJ, Wyndham CRC. Electrophysiologic evaluation of the efficacy of ethmozine in patients with ventricular tachycardia (abstr). *JACC 1984;3:537.*

7. Mann DE, Luck JC, Herre JM, Magro SA, Yepsen SC, Griffin JC, Pratt CM, Wyndham CRC. Electrophysiologic effects of ethmozin in patients with ventricular tachycardia. *Am Heart J 1984;107:674–679.*

8. Calvo R, Saksena S, Barr MJ. Electrophysiologic effects, efficacy and safety of oral moricizine hydrochloride in sustained ventricular tachycardia (abstr). *Clin Pharmacol Ther 1985;37:186.*

9. Miura DS, Wynn J, Torres V, Laux B, Keefe D, Somberg J. Antiarrhythmic efficacy of ethmozine in patients with ventricular tachycardia as determined by programmed electrical stimulation. *Am Heart J 1986;111:661–666.*

10. Dorian P, Echt DS, Mead RH, Lee JT, Lebsack CS, Winkle RA. Ethmozine: electrophysiologic, hemodynamics, and antiarrhythmic efficacy in patients with life-threatening ventricular arrhythmias. *Am Heart J 1986;112:327–332.*

11. Horowitz LN, Greenspan AM, Spielman SR, Webb CR, Morganroth J, Rotmensch H, Sokoloff NM, Rae AR, Segal BL, Kay HR. Usefulness of electrophysiologic testing in evaluation of amiodarone therapy for sustained ventricular tachyarrhythmias associated with coronary heart disease. *Am J Cardiol 1985; 55:367–371.*

12. Greenspan AM, Spielman SR, Webb CR, Sokoloff NM, Rae AP, Horowitz LN. Efficacy of combination therapy with mexiletine and a type IA agent for inducible ventricular tachyarrhythmias secondary to coronary artery disease. *Am J Cardiol 1985;56:277–284.*

13. Webb CR, Morganroth J, Senior S, Spielman SR, Greenspan AM, Horowitz LN. Flecainide: steady state electrophysiologic effects in patients with remote myocardial infarction and inducible sustained ventricular arrhythmia. *JACC 1986;8:214–220.*

Noncardiac Adverse Effects and Organ Toxicity of Moricizine During Short- and Long-Term Studies

Harold L. Kennedy, MD, MPH

To determine the tolerance and safety of moricizine, the incidence and nature of its noncardiac adverse effects and organ toxicity reported during short- and long-term clinical studies were examined. From a pooled data base of 1,256 adult patients and healthy subjects, the most frequent noncardiac adverse events were gastrointestinal (nausea) and neurologic (dizziness) complaints which occurred in 10 to 15% of patients during short-term (<3 months) studies and increased to 20 to 25% during long-term (>12 months) studies. Adverse effects led to discontinuation of moricizine therapy in 116 patients (9%). Organ toxicity consisted predominantly of drug fever, possible thrombocytopenia and elevated liver function tests and was quite low (<0.7%) for both short- and long-term studies. Moricizine appears to be a well-tolerated antiarrhythmic drug with low occurrence of noncardiac adverse effects without significant serious organ toxicity.

(Am J Cardiol 1990;65:47D–50D)

From the Division of Cardiology, Department of Internal Medicine, St. Louis University Medical Center, Saint Louis, Missouri.

Address for reprints: Harold L. Kennedy, MD, MPH, Division of Cardiology, St. Louis University School of Medicine, 3635 Vista at Grand Boulevard, St. Louis, Missouri 63110-0250.

Discovering well-tolerated and efficacious antiarrhythmic pharmacologic agents has been the goal of many clinical investigations for more than a decade. Although original interest was directed at the antiarrhythmic efficacy of each drug in various patient populations (patients with benign, potentially lethal and malignant ventricular arrhythmias), recent attention has focused on drug safety and tolerance as a result of the deleterious effects reported with some antiarrhythmic agents from the Cardiac Arrhythmia Suppression Trial.[1] Antiarrhythmic drug safety (and thus tolerance) is assessed by the incidence of (1) noncardiac adverse effects; (2) organ toxicity; (3) cardiac adverse effects (proarrhythmia, congestive heart failure and conduction changes); (4) morbidity outcomes; and (5) deaths that occur during therapy with a specific agent.

Moricizine hydrochloride has been reported to be both efficacious and safe in previous clinical investigations.[2,3] This article reviews the noncardiac adverse effects and organ toxicity observed and reported during moricizine clinical trials.

NONCARDIAC ADVERSE EFFECTS

One thousand-two hundred and fifty-six adult patients and healthy subjects who received moricizine during clinical trials constitute the data base of adverse experience collected by the E.I. Du Pont de Nemours & Company, Inc. (Table I).[4] An adverse effect was defined as any adverse experience, and therefore includes those that were definitely, possibly or probably moricizine-related, and of unknown relation.

Short-term studies: Evaluation of all patients who received moricizine up to 14 days during short-term studies were assessed for noncardiac adverse effects that occurred in ≥2% of the entire population and are listed in Table II. These data do not include electrocardiographic or laboratory abnormalities. The most frequent adverse effects were dizziness (15.1%) and nausea (9.6%) (Table II). When these data are stratified by daily dose groups (<600, 600 to 900, and >900 mg/day), dizziness and nausea continue to be the most frequently observed adverse effects (Table III). Some patients were treated with more than 1 dose and are therefore included in the more than 1 dose group. There was no relation of any specific noncardiac adverse effect to the group receiving daily doses.

Comparative studies of 1,072 patients with ventricular arrhythmias who received moricizine compared with placebo, quinidine, disopyramide and propranolol are

TABLE I Clinical Characteristics of Subjects Studied

	No. of Subjects
Subjects without arrhythmia (includes 148 healthy subjects and 3 patients with cardiovascular disease)	151
Patients with only supraventricular arrhythmia	33
Patients with ventricular arrhythmias	1,072
Benign ventricular arrhythmias	99
Potentially lethal ventricular arrhythmias	576
Lethal ventricular arrhythmias	397

TABLE II Percent of Patients Having Any Adverse Effect

Adverse Effect	Percent Unknown, Possibly, Probably, or Definately Moricizine-Related (n = 1,256)
Dizziness	15.1
Nausea	9.6
Headache	8.0
Fatigue	5.9
Palpitations	5.8
Dyspnea	5.7
Sustained ventricular tachycardia	4.3
Hypoesthesias	3.5
Abdominal pain	3.2
Dyspepsia	3.1
Vomiting	3.1
Sweating	2.9
Cardiovascular chest pain	2.8
Asthenia	2.7
Chest pain (noncardiovascular)	2.6
Nervousness	2.5
Ventricular tachycardia (length of run unspecified)	2.5
Paresthesias	2.4
Cardiac failure	2.4
Upper extremity musculoskeletal pain	2.2
Diarrhea	2.2
Dry mouth	2.1
Death (cardiovascular)	2.1
Sleep disorder	2.1

listed in Table IV. Dizziness and nausea, while 2 to 2.5 times more frequent than placebo in patients receiving moricizine, were not the dominant noncardiac adverse effects for other drugs. Quinidine was associated with a high incidence of diarrhea (22.7%); disopyramide was associated with frequent dry mouth (35.5%) and urinary retention (12.9%); and propranolol was associated with frequent headaches (16.7%), fatigue (12.5%) and blurred vision (12.5%) (Table IV).

Long-term studies: Examination of all 1,256 patients who received moricizine in the data base with regard to noncardiac adverse effects and time of first occurrence is presented in Table V. As can be noted, noncardiac adverse effects were most prevalent (45%) during the second to seventh day of therapy and this was true for all systems involved (Table V). Nevertheless, there seemed to be rather flat variation up to >2 years, except for generalized complaints.

Cautious interpretation of these data are warranted because the time intervals are not of equal duration. Additionally, other factors also must be weighed. Randomly occurring noncardiac adverse effects unrelated to moricizine would tend to occur in patients observed for longer durations, and may account for the increase in generalized complaints. Patients who demonstrated efficacy to tolerate moricizine continued to take the drug if permitted by protocol design. Critically ill patients were more likely to experience serious cardiovascular adverse effects in the first week or month of moricizine therapy because of the natural history of their cardiac disease, whereas patients with less serious cardiovascular disease were more likely to respond to moricizine and receive treatment for longer durations.

Two smaller clinical studies have reported adverse effects with moricizine therapy in patients treated for 1 year or more.[5,6] During the 1-year follow-up phase of 77 patients in the Cardiac Arrhythmia Pilot Study, the most frequently reported adverse effects were gastrointestinal or neurologic complaints which were approximately the same as placebo (exept for dizziness) (Table VI).[5] Similarly, we have followed 28 patients for 1 to 56 months

TABLE III Noncadiac Adverse Effects with Daily Dose of Moricizine

			Moricizine Daily Dose*					
			Low (<600 mg)		Middle (600–900 mg)		High (>900 mg)	
Adverse Effects	No. of Pts.	%	n	%	n	%	n	%
Total No. of Pts.	1,256		257		948		377	
Dizziness	188	15.0	63	24.5	93	9.8	49	13.0
Nausea	119	9.5	35	13.6	70	7.4	24	6.4
Hypoesthesias	93	7.4	40	15.6	30	3.2	24	6.4
Headache	80	6.4	17	6.6	55	5.8	16	4.2
Pain	54	4.3	17	6.6	29	3.1	9	2.4
Fatigue	46	3.7	12	4.7	29	3.1	9	2.4
Dyspnea	40	3.2	6	2.3	27	2.8	10	2.7
Dry mouth	26	2.1	4	1.6	15	1.6	8	2.1
Vomiting	26	2.1	5	1.9	21	2.2	6	1.6

* Duration of 1 to 14 days.

TABLE IV Comparative Noncardiac Adverse Effects of Patients with Ventricular Premature Complexes

	Ethmozine*		Placebo*		Quinidine*		Disopyramide*		Propranolol*	
Adverse Effect	n	%	n	%	n	%	n	%	n	%
Total No. of Pts.	1,256		618		110		31		24	8.3
Dizziness	121	11.3	33	5.3	8	7.3	—		2	
Nausea	74	6.9	18	2.9	7	6.4	3	9.7	—	
Headache	62	5.8	27	4.4	—		—		4	16.7
Pain	41	3.8	31	5.0	6	5.5	2	6.5	—	
Dyspnea	40	3.8	22	3.6	—		—		—	
Hypoesthesias	33	3.7	—		3	2.7	—		—	
Fatigue	22	3.1	16	2.6	6	5.5	2	6.5	3	12.5
Vomiting	—	2.1	—		—		—		—	
Dry mouth	—		—		—		11	35.5	—	
Nervousness	—		—		—		3	9.7	—	
Blurred vision	—		—		3	2.7	2	6.5	3	12.5
Diarrhea	—		—		25	22.7	—		—	
Constipation	—		—		—		2	6.5	—	
Somnolence	—		—		—		—		2	8.3
Urinary retention			—		—		4	12.9	—	

* Duration of 1 to 14 days.

TABLE V Percent of Subjects with Adverse Effects According to Duration of Moricizine Therapy

	Time of Occurrences										
Effects	Day 1	Day 2–7	Day 8–14	Day 15–30	Day 31–90	Mo 3–6	Mo 6–12	Yrs 1–1.5	Yrs 1.5–2	Yrs >2	Total
Subjects at risk (no.)	1,256	1,210	682	567	437	344	291	221	153	106	1,256
Subjects with adverse effects (%)	21.3	45.2	27.1	34.6	40.5	37.8	41.2	33.9	24.8	50.9	71.5
Nervous system (%)	10.5	16.9	8.8	8.5	11.2	11.6	11.3	10.9	7.2	14.2	37.7
Digestive system (%)	6.1	14.8	7.5	8.1	11.4	8.1	14.1	6.3	4.6	14.2	29.6
Generalized complaints (%)	4.7	10.84	6.7	11.6	11.2	10.8	12.4	8.1	3.9	17.0	28.7
Respiratory system (%)	1.3	4.8	3.7	4.6	10.1	9.9	13.1	8.1	9.2	13.2	17.9
Muscoloskeletal system (%)	0.6	3.0	1.9	5.6	4.6	3.8	6.9	3.6	2.0	9.4	10.8
Dermatologic system (%)	1.0	2.4	1.9	2.6	3.2	3.8	2.7	4.5	2.6	2.8	8.8
Urogenital system (%)	0.4	1.0	0.9	2.3	4.6	2.9	3.1	4.1	2.0	5.7	7.1

(mean 25 ± 17) and reported late noncardiac adverse effects in 21% of patients, with gastrointestinal (11%) and neurologic (7%) complaints dominating.[6]

Adverse effects leading to discontinuation: Examination of all 1,256 patients who received moricizine during short-term studies showed that adverse effects led to discontinuation in 116 patients (9%). The most frequent noncardiac adverse effects leading to discontinuation were gastrointestinal (2.9%) and neurologic (0.6%) (Table VII). These complaints have also dominated the limited long-term experience for discontinuation of moricizine.[5,6]

ORGAN TOXICITY

Moricizine organ toxicity has been assessed by laboratory testing (hematology, blood chemistry and urinalysis), chest x-rays, and ophthalmic examinations obtained at specified times during both short- and long-term clinical trials.[4] The dominant organ toxic effects found during moricizine therapy are shown in Table VIII. Drug-related fever that occurred in 3 patients resolved within 48 hours after discontinuation of moricizine. All 3 patients were again given moricizine; fever recurred and was unrelated to dose. Thrombocytopenia without evidence of bone marrow toxicity occurred in 2 patients, and both patients were being treated concomitantly with other drugs known to cause thrombocytopenia, and therefore the relation to moricizine is unknown. Elevated liver func-

TABLE VI Noncardiac Adverse Effects Occurring in the Cardiac Arrhythmia Pilot Study During One Year of Moricizine Therapy

	Patients with Adverse Effects	
Adverse Effects	Moricizine (n = 77)	Placebo (n = 87)
Dizziness	10	0*
Respiratory	8	5
Cutaneous	6	3
Gastrointestinal	26	21
Genitourinary	18	11
Neurologic	34	38
Other	44	43

* p = 0.0004.

TABLE VII Adverse Effects Leading to Discontinuation of Moricizine Therapy in 1,256 Patients

Reasons for Discontinuation in ≥ Two Patients	Patients* n	Patients* %
Cardiovascular		
Electrocardiographic changes	17	1.4
Congsetive heart failure	11	0.9
Atrial fibrillation	4	0.3
Gastrointestinal		
Nausea	34	2.7
Gastrointestinal upset	3	0.2
Neurologic		
Anxiety	3	0.2
Paresthesias/hypoesthesias	2	0.2
Hand tremors	2	0.2
Respiratory		
Dyspenea	2	0.2
Renal		
Urinary retention	4	0.3
Other		
Laboratory abnormalities	5	0.4
Drug fever	3	0.2
Blurred vision	3	0.2

* Moricizine discontinued in 116 of 1,256 patients (9%).

tion tests during moricizine therapy consistent with drug-induced hepatotoxicity occurred in 6 patients. Liver function tests returned to normal after discontinuation of moricizine in 3 patients, and 3 patients had unreported follow-up.[4]

In addition, 8 of 1,256 patients had renal failure reported as an adverse effect, which included 6 patients with severe congestive heart failure and 2 patients with carcinoma of the bladder. Extrapyramidal adverse effects have not been reported with moricizine, although it is a phenothiazine derivative. Moricizine has not been reported to cause galactorrhea or gynecomastia, and sexual dysfunction has been rarely reported.[4] Long-term clinical studies of small patient groups have not disclosed time-dependent organ toxicity.[5,6] Thus, both short- and long-term adverse experiences indicate limited evidence of organ toxicity.

TABLE VIII Organ Toxic Effects Occurring During Moricizine Therapy

Clinical Toxicity	No. of Pts. with Paired Data	Duration of Moricizine (Days)	Pts. with Toxicity
Drug fever	1,256	14–147	3 (0.2%)
Decreased platelet counts*	1,105	6–448	2 (0.2%)*
Elevated SGOT,† SGPT,† and/or bilirubin‡	1,105	6–214	8 (0.7%)‡

* ≤100,000/mm.
† More than fivefold increase above upper limit of normal range.
‡ More than twofold increase above upper limit of normal range.
SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

CLINICAL IMPLICATIONS

Thus, the early experience with moricizine antiarrhythmic therapy indicates that noncardiac adverse effects predominantly consist of gastrointestinal (nausea) and neurologic (dizziness) complaints which occurred in 10 to 15% of patients during short-term studies and increased to 20 to 25% in long-term studies.[2–6] Organ toxicity was admirably low (<0.7%) for both short- and long-term studies.[4] These data confirm that moricizine is a well-tolerated antiarrhythmic drug without significant toxicity.

REFERENCES

1. The Cardiac Arrhythmia Suppression Trial Investigators. Preliminary report: effects of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med 1989;321:406–412.*
2. Pratt CM, Yepsen SC, Taylor AA, Mason DT, Miller RR, Quinones MA, Lewis RA. Ethmozine suppression of single and repetitive ventricular premature depolarizations during therapy: documentation of efficacy and long-term safety. *Am Heart J 1983;106:85–91.*
3. Morganroth J, Pratt CM, Kennedy HL, Singh SN, Platt ML, Baker BJ, Mason DT. Efficacy and tolerance of ethmozine (moricizine HCl) in placebo-controlled trials. *Am J Cardiol 1987;60:48F–51F.*
4. Investigators Data of E.I. Du Pont de Nemours & Company prepared for the *FDA Cardio-Renal Advisory Committee, January 27, 1989.*
5. The Cardiac Arrhythmia Pilot Study Investigators. Effect of encainide, flecainide, imipramine and moricizine on ventricular arrhythmias during the year after acute myocardial infarction: the CAPS. *Am J Cardiol 1988;61:501–509.*
6. Kennedy HL, Sprague MK, Homan SM, Seiler SM, Wiens RD, Janosik DL, Redd RM, Buckingham TA. The natural history of potentially lethal ventricular arrhythmias in patients treated chronically with antiarrhythmic drug therapy. *Am J Cardiol 1989;64:1289–1297.*

Proarrhythmic Potential of Moricizine: Strengths and Limitations of a Data Base Analysis

Craig M. Pratt, MD

Moricizine was studied in 908 patients with ventricular arrhythmias. A proarrhythmia occurred in 29 (3.2%). When the severity of the proarrhythmia and the type of presenting ventricular arrhythmia were correlated, no proarrhythmic events occurred in patients who presented with benign ventricular arrhythmias. Four deaths were attributed to the proarrhythmic effects of moricizine. Of these, 3 occurred in patients presenting with lethal ventricular arrhythmias. A total of 15 serious proarrhythmic events occurred, all of which resolved without lethal consequence. The overall proarrhythmia incidence in the lethal and potentially lethal ventricular arrhythmia categories was not different (3.2 vs 3.7%, respectively). Thus, a proarrhythmia occurred in patients with more advanced structural heart disease, and occurred almost exclusively in patients who presented with potentially lethal or lethal ventricular arrhythmia. There was no relation between the dose of moricizine and the incidence of proarrhythmic events. Of the 29 proarrhythmic events, 26 occurred within 7 days (90%) of the initiation of moricizine therapy. Thus, moricizine appears to have a low proarrhythmic potential in the populations tested, including patients presenting with lethal ventricular arrhythmias. The implications of the Cardiac Arrhythmia Suppression Trial on such a data base analysis are discussed.

(Am J Cardiol 1990;65:51D–55D)

From the Section of Cardiology, Department of Internal Medicine, Baylor College of Medicine, and The Methodist Hospital, Houston, Texas.

Address for reprints: Craig M. Pratt, MD, Baylor College of Medicine, Director, Coronary Care Unit, The Methodist Hospital, 6535 Fannin MS F1001, Houston, Texas 77030.

Since the recent publication of our evaluation of the low proarrhythmic potential of moricizine based on the analysis of the American Du Pont data base,[1] there has been a major breakthrough in arrhythmia research. Although the proarrhythmia report was published in February 1989 in *The American Journal of Cardiology*, these results were soon followed by the revelation that both encainide and flecainide increased arrhythmic death/cardiac arrest mortality in patients with ventricular arrhythmias surviving acute myocardial infarction.[2] The primary finding of the Cardiac Arrhythmia Suppression Trial (CAST) was a 3.64-fold increase in arrhythmic death/cardiac arrest mortality with these 2 electrophysiologic type 1C agents. A joint press conference was held by the National Heart, Lung, and Blood Institute in cooperation with the Food and Drug Administration (FDA) on April 25, 1989, communicating the danger of these 2 antiarrhythmic agents in patients similar to the CAST population. The encainide and flecainide limbs of the CAST were discontinued, and patients were reevaluated for consideration of alternative therapy. Moricizine is the only active treatment limb remaining in the CAST.

The proarrhythmic mortality detected in the CAST will inevitably compel clinicians to reassess the indications for antiarrhythmic therapy, while focusing increased interest on the 1 active antiarrhythmic drug remaining in the CAST: moricizine. Therefore, it is appropriate at this time to review the results of our evaluation of the proarrhythmic potential of moricizine, reflecting on the implications of our data base approach to the study design issues that were responsible for the CAST results.

REVIEW OF THE DU PONT DATA BASE: PROARRHYTHMIA WITH MORICIZINE

Methods: This study represented a review of the 908 patients treated with moricizine for ventricular arrhythmias.[1] Data were derived from the results of Holter recordings, a review of the patients' case report forms, and review of the adverse drug experience report forms sent to the FDA. Although the data were retrospectively analyzed, the treatment results of each patient were analyzed by prospective definitions of proarrhythmia, as well as a prospective classification of the patients' presenting ventricular arrhythmia before initiation of moricizine therapy.

Definitions of presenting arrhythmia: A patient was considered to have a benign ventricular arrhythmia if ventricular premature complexes (VPCs) and nonsustained ventricular tachycardia (VT) occurred in patients

TABLE I Definitions of Proarrhythmia for Ventricular Arrhythmias

Proarrhythmic death
Serious proarrhythmia events
  Spontaneous new onset of sustained or polymorphic VT, VFL or VF
  Spontaneous new onset of hemodynamically significant nonsustained VT or, if no hemodynamic significance, ≥100 VT events/day
Nonserious proarrhythmic events
  Asymptomatic change in the frequency of previously documented VPCs or nonsustained VT including:
  Increase in the frequency of VPCs required for proarrhythmia (except when due predominantly to sustained VT)

Mean VPCs/Hour

Baseline	Fold Increase
10–50	30
51–100	15
101–300	5
301–500	4
501–1,000	3
>1,000	2

Increase in frequency of VT events required for proarrhythmia

VT Events/Day

Baseline	Fold Increase
1	≥100
2–5	50
6–50	20
>50	10

Or a change from no symptoms or palpitations or presyncope to syncope, cardiac arrest or death

VF = ventricular fibrillation; VFL = ventricular flutter; VPC = ventricular premature complex; VT = ventricular tachycardia.

with no organic heart disease and were either asymptomatic or mildly symptomatic. Patients with potentially lethal ventricular arrhythmias were defined as those with asymptomatic or mildly symptomatic ventricular arrhythmia and structural heart disease. Patients with lethal ventricular arrhythmias were defined as those who presented with sustained VT or a ventricular arrhythmia requiring emergency intervention or cardioversion, or which culminated in ventricular flutter/fibrillation, or caused other hemodynamic consequences leading to syncope, seizure or cardiovascular collapse. For the purpose of this analysis, VT was defined as ≥3 consecutive VPCs at a rate of ≥100 beats/min. Sustained VT was defined as a run of VT lasting at least 30 seconds or requiring intervention.

Definitions of proarrhythmia: The thrust of our classification system of proarrhythmia was to devise categories of increasing clinical importance. Although it has been recognized that all antiarrhythmic drugs can cause an increase (rather than the desired decrease) in spontaneous VPCs and nonsustained VT, the prognostic significance of these observations is unclear. Therefore, the intent of this classification system was to clearly separate the observed increases in VPC and VT frequency from more prognostically important categories. The increase required in VPC or VT events to document proarrhythmia was defined from a previous analysis of spontaneous VPC and VT variability using 3,854 Holter recordings in 630 patients from the Du Pont data base.[3] The definitions and clinical divisions of proarrhythmia are listed in Table I.

Proarrhythmic events that consisted only of an increased frequency of VPCs (see Table I) or runs of nonsustained VT or the new onset of nonsustained VT without any hemodynamic consequences were all defined as nonserious proarrhythmic events. Patients were considered to have a serious proarrhythmic event if the new onset of nonsustained VT produced a hemodynamically significant symptom such as syncope. Similarly, if the new onset of sustained VT, torsades de pointes VT or ventricular flutter/fibrillation were detected but did not produce a hemodynamically significant event, they were classified as serious proarrhythmic events. The remaining category was proarrhythmic death, defined as an observed ventricular arrhythmia within 14 days of the initiation of or change in the dose of moricizine that resulted in arrhythmic death. This 14-day cutoff was based on previous arrhythmia data base observations,[4] and although reasonable, has limitations that will be discussed.

TABLE II Number of Patients by Ventricular Arrhythmia Classification and Proarrhythmic Categories

Classification of Ventricular Arrhythmias	Pts. (n = 908)	Proarrhythmic Category		
		Death (n = 4)	Serious (n = 15)	Nonserious (n = 10)
Benign	89	0	0	0
Potentially lethal	509	1 (0.2%)	14 (2.8%)	4 (0.8%)
Lethal	310	3 (1.0%)	1 (0.3%)	6 (1.9%)

MORICIZINE PROARRHYTHMIA DATA BASE RESULTS

Incidence of proarrhythmia with moricizine: Of the 908 patients with ventricular arrhythmias treated with moricizine, 29 (3.2%) had a proarrhythmic event. The distribution of these events by the classification of presenting arrhythmias and the severity of the proarrhythmic event is given in Table II. No proarrhythmic events were detected in patients presenting with benign ventricular arrhythmia and the incidence of proarrhythmic events was low in patients with potentially lethal as well as lethal arrhythmias, with no difference between the 2 categories (3.2 and 3.7%, respectively). A total of 15 patients had serious proarrhythmic events. This included 2 patients with a new onset of sustained VT that produced a hemodynamically significant outcome, 9 patients with a new onset of sustained VT without hemodynamic consequence, and 1 case of torsades de pointes VT that had not been previously detected. Additionally, 2 patients had a new onset of ventricular flutter/fibrillation and 1 patient had syncope. Of the 10 cases considered nonserious proarrhythmic events, only 1 was due to an increased VPC frequency exceeding the limits mentioned in Table I, whereas 9 were due to an increased frequency of VT events. Of the 15 patients with serious proarrhythmic events, all recovered without residual adverse effects. Of these, 60% did not require medical intervention, whereas

3 patients required treatment with intravenous antiarrhythmic drugs and 3 required electrical cardioversion. Three of 4 cases classified as proarrhythmic death during moricizine therapy were in patients presenting with a lethal arrhythmia. Thus, the proarrhythmic death rates were 0, 0.2 and 1.0% for patients presenting with benign, potentially lethal and lethal arrhythmias, respectively.

Demographic characteristics and time course of moricizine proarrhythmia: Most patients in whom a proarrhythmia developed while taking moricizine were men (25 of 29), and most of these were white (22 of 25). The mean age was 60 years, and the daily dose of moricizine ranged from 8 to 15 mg/kg (600 to 1,200 mg/day). All but 1 of these 29 patients had received prior antiarrhythmic therapy. Patients with more serious proarrhythmia tended to be older than patients with nonserious proarrhythmia (66 vs 44 years, $p < 0.05$).

Although serious proarrhythmia during moricizine dosing occurred more often in older patients, there was no relation between the total daily dose of moricizine and the incidence of proarrhythmia. As previously mentioned, the temporal definition of a proarrhythmia required events to take place within 14 days of initiation of therapy or dose change. In terms of the prospective definition, in the opinion of most investigators, it was considered unlikely that moricizine was causal when arrhythmic events occurred after that time. Of the 29 proarrhythmic events that occurred within 14 days, 90% occurred within the first 7 days. A listing of the number of proarrhythmic events by category and duration of moricizine dosing is listed in Table III. No proarrhythmic deaths were noted in the second week of moricizine dosing. Patients experiencing proarrhythmic events during moricizine therapy tended to have more significant organic heart disease, including those with a history of coronary artery disease, congestive heart failure, prior myocardial infarction and electrocardiographic abnormalities at rest. In contrast, there was no statistically significant association of proarrhythmia with moricizine compared with the baseline frequency of VPCs or the baseline electrocardiogram with reference to PR, QRS or QT interval duration.

TABLE III Number of Proarrhythmic Events by Category and Duration of the Moricizine Dose at Which the Event Occurred

Proarrhythmia Category	Days on the Moricizine Dose at Which Proarrhythmia Occurred										
	1	2	3	4	5	6	7	8	9	10	Total
Death	—	1	1	—	1	—	1	—	—	—	4
Serious	1	3	4	1	2	1	—	2	—	1	15
Other	3	3	—	—	2	1	1	—	—	—	10
Total	4	7	5	1	5	2	2	2	0	1	29

DISCUSSION

The evaluation of the pharmacologic data base of an antiarrhythmic drug represents an attempt to analyze uniformly the entire experience with that agent in order to estimate more accurately its proarrhythmic potential. Unfortunately, this approach has limitations, which were identified by the CAST. However, one advantage of the approach is that it uses uniform prospective definitions of the presenting ventricular arrhythmia and the seriousness of the proarrhythmia produced, which are applied to the entire pharmaceutical experiential data base. This approach is clearly preferable to the smaller studies from individual investigators that use a variety of definitions. Furthermore, in the moricizine proarrhythmia data base, Holter proarrhythmia definitions were derived directly from the patients' placebo (control) Holter recordings; thus, the variability limits listed in Table I are unique in that they are derived from within this data base.[3]

Evolution of the concept of proarrhythmia: In our analysis of the moricizine data base, we chose to use a 14-day treatment limit for the prospective definition of the proarrhythmic effects of moricizine. This was based on observations from published studies that antiarrhythmic drugs are usually thought to induce potentially life-threatening ventricular arrhythmias within the first few days or weeks.[4,5] These observations have been made over decades, including an analysis of 31 cases of torsades de pointes VT caused by quinidine, in which most of these episodes occurred in the first few days.[6] Recent observations of patients with life-threatening ventricular arrhythmias treated with a variety of antiarrhythmic drugs reported a 3-day mean time for the development of drug-associated sustained VT/fibrillation.[5]

The CAST mortality result: is it a new type of proarrhythmia? Over an average of 10 months of therapy with encainide or flecainide, there was a 3.64-fold increase in arrhythmic death/cardiac arrest compared with the placebo group in the CAST. Because there was a parallel placebo group throughout this treatment period, it was possible to demonstrate that there was an excessive number of arrhythmic deaths throughout the study, rather than simply during the first days after initiation of therapy. In fact, patients randomized in the CAST had already undergone the usual surveillance for proarrhythmia in that they had been tested with encainide or flecainide for an average of 2 weeks (open-label phase) and had documented VPC suppression (≥80% VPC reduction) compared with baseline. Thus, the excessive number of arrhythmic deaths during therapy with flecainide and encainide in the CAST is all the more surprising since the usual methods of screening for proarrhythmia were performed in every patient before randomization. This observation of an excessive arrhythmic mortality in patients already proven to tolerate these drugs and to be "suppressors" is especially troublesome; it also dispels our temporal preconception of proarrhythmia.

Suggested mechanisms of encainide/flecainide proarrhythmia in the CAST: It has been suggested that the mechanism by which antiarrhythmic drugs induce life-threatening ventricular arrhythmias is their electrophysiologic properties of slowing conduction in diseased areas of the myocardium. This potentially enhances the possibility of reentrant sustained VT.[7] Rinkenberger et al[8] postulated that antiarrhythmic drugs may facilitate the initiation of sustained VT, significantly prolonging acti-

vation while minimally increasing refractoriness, effects that may be accentuated during ischemia. Animal models form the basis of this concept. In a landmark paper by Nattel et al,[9] pretreatment with aprindine in a canine infarction model greatly increased the incidence of sustained VT during repeat acute ischemic events compared with no pretreatment. Thus, pretreatment with an antiarrhythmic drug before coronary occlusion was, in this animal model, "proarrhythmic." Patients randomized in the CAST did not have any systematic baseline evaluation of exercise-induced ischemia, making retrospective assessment of that variable difficult. However, perhaps patients in the CAST, like the animal model counterpart, had a decreased fibrillation threshold during acute ischemic events in the presence of myocardial scarring, enhanced by the presence of flecainide and encainide. These 2 agents also have a significant negative inotropic effect, which may contribute to the observed proarrhythmic effect.[10]

Limitations of data base analysis for estimating proarrhythmia incidence: In previous reviews of the data bases of flecainide and encainide, Morganroth[11] concluded that proarrhythmic events are much more likely to occur in the setting of structural heart disease, sustained VT and rapid-dose escalation of the class 1C drugs. The moricizine data base is similar in that serious proarrhythmia or proarrhythmic death with moricizine was limited to patients with structural heart disease, usually seen in patients presenting with lethal ventricular arrhythmias. There appears to be no dose-related increase in proarrhythmia rates with moricizine.[1]

What is troubling is why the analysis of the data bases of encainide (n = 1,755) and flecainide (n = 1,330) did not detect or at least raise suspicion of the high incidence of proarrhythmia in patients presenting with "potentially lethal" arrhythmias, subsequently discovered in the CAST. By the classification system used in those data base studies, the CAST population would be in the potentially lethal category. Yet the CAST encainide/flecainide population had a 4.4% arrhythmic death mortality at 10 months, higher than the estimated incidence for patients presenting with lethal arrhythmias in the flecainide/encainide data base studies.[11]

It is likely that this large mortality discrepancy is primarily the result of 2 factors. I believe the most important factor is that the CAST population represented a group of patients not included in pharmaceutical drug data base experiences (i.e., patients with recent acute myocardial infarction are almost always excluded from pharmaceutical studies). One could speculate that the unique proarrhythmia discovered in the CAST is due to sporadic recurring episodes of acute ischemia in the CAST population that would not occur in other patient populations. This is an important comparative point. In the flecainide data base, 13 of the 14 sudden deaths attributed to flecainide occurred in less than 14 days,[4] the cutoff used in our analysis of the moricizine data base.[1] This leads to what I consider the second major difference between a data base approach compared with design: the presence of a parallel placebo group throughout the entire treatment interval in the CAST. In general, parallel placebo groups are only used in pharmaceutical studies in patients with benign ventricular arrhythmia, not in patients with potentially lethal or lethal-presenting ventricular arrhythmias. Thus, the CAST design allowed the demonstration of the unusual temporal profile of this proarrhythmia.

Extrapolation of moricizine proarrhythmia data base to the CAST: Whereas the CAST[2] and other recent studies[11] have generated a healthy skepticism about the risk-benefit ratio of all antiarrhythmic drugs in patients with potentially lethal arrhythmias, one should not overreact and extrapolate these results to all patient populations or all antiarrhythmic drugs.

The results of this moricizine proarrhythmia analysis are still reassuring and promising in several ways. First, we have reported an extraordinarily low incidence of proarrhythmic death during 14 days with moricizine, both in patients with potentially lethal and lethal-presenting arrhythmias (0.2 and 1.0%, respectively). Second, moricizine is unusually well tolerated in patients with congestive heart failure or evidence of left ventricular dysfunction, or both, where it frequently still achieves VPC suppression.[12] Also, the moricizine data base is made up almost entirely of patients at increased risk of sudden death, with only a small proportion ($\cong$10%) of patients with benign VPCs.

The most important reason for optimism is the fact that moricizine continues to be the only remaining active antiarrhythmic agent used in the CAST. It is the only antiarrhythmic agent (available or investigational) that is being subjected to the scrutiny of a placebo-controlled trial in a postinfarction population.[2] Furthermore, because of the interim CAST results, randomization is now limited to patients at even higher risk (left ventricular ejection fraction $\leq$40% within 90 days of acute myocardial infarction). As with all multicenter National Heart, Lung, and Blood Institute trials, a Policy and Safety Monitoring Board intermittently reviews all safety issues in the trial. It was this monitoring board that recommended the discontinuation of encainide and flecainide, while recommending the continuation of the moricizine limb and its respective placebo. Moricizine has thus far been judged safe relative to proarrhythmia in the CAST. One hopes that moricizine will not only prove to be safe, but also beneficial.

REFERENCES

1. Morganroth J, Pratt CM. Prevalence and characteristics of proarrhythmia from moricizine (Ethmozine®). *Am J Cardiol 1989;63:172–176.*
2. The Cardiac Arrhythmic Suppression Trial CAST Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med 1989;321: 406–412.*
3. Morganroth J, Borland M, Chao G. Application of frequency definition of ventricular proarrhythmia. *Am J Cardiol 1987;59:97–99.*
4. Morganroth J, Anderson JL, Gentzkow GD. Classification by type of ventricular arrhythmia predicts frequency of adverse cardiac events from flecainide. *JACC 1986;8:607–615.*
5. Minardo JD, Hager JJ, Miles WM, Zipes DP, Prystowsky EN. Clinical characteristics of patients with ventricular fibrillation during antiarrhythmic drug therapy. *N Engl J Med 1988;319:257–262.*

6. Bauman J, Bauernfeind R, Hoff J, Strasberg B, Swiryn S, Rosen K. Torsades de pointes due to quinidine: observations in 31 patients. *Am Heart J 1984; 107:425–430.*
7. Winkle RA, Mason JW, Griffin JC, Ross D. Malignant ventricular tachyarrhythmias associated with the use of encainide. *Am Heart J 1981;102:857–864.*
8. Rinkenberger RL, Prystowsky EN, Jackman WM, Naccarelli GV, Hager JJ, Zipes DP. Drug conversion of nonsustained ventricular tachycardia to sustained ventricular tachycardia during serial electrophysiologic studies: identification of drugs that exacerbate tachycardia and potential mechanisms. *Am Heart J 1982;103:177–184.*
9. Nattel S, Pedersen DH, Zipes DP. Alterations in regional myocardial distribution arrhythmogenic effects of aprindine produced by coronary artery occlusion in the dog. *Cardiovasc Res 1981;15:80–85.*
10. Pratt CM, Eaton T, Francis M, Woolbert S, Mahmarian J, Roberts R, Young JB. The inverse relationship between baseline left ventricular ejection fraction and outcome of antiarrhythmic therapy: a dangerous imbalance in the risk-benefit ratio. *Am Heart J 1989;118:433–440.*
11. Morganroth J. Risk factors for the development of proarrhythmic events. *Am J Cardiol 1987;59:32E–37E.*
12. Pratt CM, Podrid P, Greatrix B, Borland M, Mahler S. Efficacy and safety of moricizine (Ethmozine®) in patients with congestive heart failure: a summary of the experience in the United States. *Am Heart J 1990; in press.*

Antiarrhythmic Drug Therapy for Congestive Heart Failure with Focus on Moricizine

Philip J. Podrid, MD, and Scott L. Beau, MD

Many patients who have serious ventricular arrhythmia requiring antiarrhythmic drug therapy have congestive heart failure (CHF). However, the pharmacokinetic and pharmacodynamic properties of the antiarrhythmic drugs are altered in the presence of CHF. It has been reported that some adverse effects, primarily aggravation of arrhythmia and CHF occur more frequently in patients with a history of left ventricular (LV) dysfunction. Moreover, antiarrhythmic drugs are less effective in patients with a history of CHF and a reduced LV ejection fraction (LVEF).

Moricizine, a new antiarrhythmic drug, has been undergoing clinical trials for over 13 years in the United States. The data base involving 1,072 patients was analyzed to establish the effect of this agent in patients with CHF. The presence of CHF does not alter the absorption, half-life and clearance of moricizine.

The incidence of CHF exacerbation definitely related to moricizine was low (2%) and occurred primarily in patients with a history of CHF. Aggravation of arrhythmia and conduction abnormalities also occurred more often in patients with prior CHF. However, the incidence of all other adverse effects involving other organ systems was the same in patients with and without CHF and was also unrelated to the baseline LVEF. The effect of moricizine for suppressing spontaneously occurring ventricular ectopy was also similar in patients with and without CHF and was independent of LVEF. However, the drug is less effective in preventing sustained ventricular arrhythmia in patients with CHF.

(Am J Cardiol 1990;65:56D–64D)

From the Department of Medicine & Section of Cardiology, Boston University Medical School, Boston, Massachusetts.

Address for reprints: Philip J. Podrid, MD, Section of Cardiology, University Hospital, 88 E. Newton Street, Boston, Massachusetts 02118.

The prevalence of congestive heart failure (CHF) in the United States is substantial, having been estimated to be present in 2 million patients.[1,2] Among patients referred for treatment of New York Heart Association (NYHA) class III or IV CHF, the mortality rate is approximately 50% in the first year, with half of these deaths occurring suddenly, presumably secondary to a ventricular arrhythmia.[3,4] With the use of more frequent extended ambulatory monitoring, it has been observed that the incidence of asymptomatic or minimally symptomatic ventricular arrhythmia in this patient population is high. A recent review[2] suggests that 85 to 90% of such patients have documented frequent ventricular premature complexes (VPCs), whereas more than 50% have runs of nonsustained ventricular tachycardia (VT). Often the physician intuitively initiates antiarrhythmic drug therapy in these patients to prevent a more serious tachyarrhythmia and sudden death. However, the association between spontaneously occurring ventricular arrhythmia and the risk of sudden death in these patients is controversial as data are conflicting.[5,6] Moreover, there are a paucity of data supporting the benefits of antiarrhythmic therapy for prolonging life by preventing such serious ventricular tachyarrhythmias. Furthermore, the pharmacokinetic and pharmacodynamic properties of antiarrhythmic drugs are altered in the patient with CHF.[7] Many of the medications used for its treatment induce physiologic and biochemical abnormalities which may interact with antiarrhythmic drug actions. There is, therefore, appropriate concern regarding the efficacy and safety of antiarrhythmic therapy in patients with CHF.

The purpose of this report is to review what is known about the efficacy, safety and toxicity of antiarrhythmic drugs when used to treat ventricular arrhythmias in patients with CHF. An important focus will be a new agent, moricizine.

SAFETY: ALTERED PHARMACOKINETICS AND PHARMACODYNAMICS

A major concern about the use of antiarrhythmic drugs relates to their adverse effects. This class of drugs has a narrow therapeutic toxic ratio, especially in patients with heart disease, and in the presence of CHF, there are a number of factors that further narrow this ratio. The pharmacokinetic properties of antiarrhythmic drugs are abnormal in patients with CHF when compared with those without left ventricular (LV) dysfunction. For most antiarrhythmic drugs studied, the volume of distribution is reduced in patients with CHF, which results in higher than usual plasma drug concentrations and requires a

reduction in dose.[8,9] During CHF, there is a decrease in renal and hepatic blood flow, which reduces the rate of metabolism and elimination of the drug or its metabolites.[9,10] This may also produce higher than expected drug concentrations and a prolonged elimination half-life. As a result, drug toxicity may occur when lower doses of the drug are administered and adverse effects may take a longer time to resolve because of the prolonged time for metabolism and elimination. The magnitude of change in these pharmacokinetic variables, however, is unpredictable in patients with CHF. Additionally, if the half-life is prolonged, a longer time will be required to reach steady state compared with that in normal subjects.[8] Plasma levels checked at the usual time, after 5 half-lives have elapsed, may be low, but escalation of drug dosage in such patients at this time may result in toxic levels a few days later. Therefore, in patients with CHF, the initial dose of drug should be decreased and more time allowed before any increase in dose.

Pharmacokinetics of moricizine in congestive heart failure: The pharmacokinetic properties of moricizine were determined in 17 patients with a history of CHF and were compared with data obtained in 65 patients without clinical failure. Pharmacokinetic parameters including maximal concentration (C_{max}), time to maximal concentration (T_{max}), area under the curve (AUC) and elimination half-life ($t_{1/2}$) were determined on day 1 of moricizine therapy and, in most cases, on the last day of dosing. There was no statistically significant difference in the values of C_{max}, T_{max}, AUC or $t_{1/2}$ at any dose level in patients with compared with those without CHF (Table I). Moricizine pharmacokinetics are thus not affected by the presence of CHF alone, although associated hepatic or renal dysfunction may alter them. These data suggest that there is no need to alter the dosage of drug administered to patients with CHF in whom hepatic and renal functions are intact. Data are not available for patients with CHF who have hepatic or renal dysfunction, but no doubt dosage reduction is required, similar to that necessary in patients with primary renal or hepatic dysfunction.

HEMODYNAMIC EFFECTS

One of the serious adverse effects of antiarrhythmic drug therapy is a worsening of LV function due to the negative inotropic activity of these agents. Most of the antiarrhythmic drugs have been reported to directly depress the contractility of the isolated muscle fibers in vitro or the intact heart in vivo.[11,12] Additionally, these drugs have peripheral vascular effects that may interact with their negative inotropic activity[12,13] (Table II). A number of studies have reported that some of these drugs can significantly alter hemodynamic parameters and can reduce LVEF measured invasively or noninvasively.[14–16] The provocation of clinically significant CHF has been observed with several of these agents.[16,17] There is substantial evidence to suggest that the negative inotropic effect of these agents is more frequently observed in patients with preexisting CHF. In a report by Ravid et al[17] involving 6 of the newer antiarrhythmic agents including moricizine, mexiletine, encainide, tocainide, lorcainide and propafenone, the overall incidence of CHF was 1.8%. However, among patients with a history of CHF the incidence was 3.9%. All but 1 of the patients with exacerbation of CHF had a previous history of CHF. Predictors of CHF exacerbation were a previous history of failure, a greatly reduced LVEF (<35%) and an underlying cardiomyopathy. The incidence of CHF provocation was 12.5% when LVEF was <35% and 0.9% in those with LVEF >35% ($p < 0.001$). The average LVEF was 22% in those in whom CHF developed compared with 39% in patients in whom it did not develop ($p < 0.001$).

TABLE I Pharmacokinetics of Moricizine in Patients With and Without Congestive Heart Failure (CHF)

	Without CHF	With CHF
Maximal concentration (μg/ml)		
Mean	0.98	1.05
Range	0.10–2.88	0.21–2.10
Time to peak levels (hrs)		
Mean	1.40	1.42
Range	0.42–3.92	0.5–3.00
Area under the curve (μg · hr/ml)		
Mean	3.14	2.97
Range	0.38–10.87	0.38–7.14
Half-life (hrs)		
Mean	2.68	3.12
Range	1.08–14.10	0.80–11.70

In a recent study involving 8 antiarrhythmic drugs (procainamide, quinidine, disopyramide, cifenline, moricizine, indecainide, metoprolol and sotolol), Pratt et al[18] reported similar data. In this retrospective review of 246 patients, of whom 101 had LVEF <40%, the development of CHF was significantly more frequent in those with LV dysfunction than in those with an intact left ventricle. Of the patients with LVEF of <40%, 11 developed CHF compared with 1 of 145 patients (0.7%) with intact LV function. The average LVEF of those in whom CHF developed was 20% compared with 45% in the patients who responded to the drugs and had no CHF ($p < 0.0001$).

There are also limited data available about the hemodynamic effects of individual oral agents.

Quinidine: Although quinidine exerts direct negative inotropic effects, it also reduces peripheral vascular resis-

TABLE II Hemodynamic Effects of Antiarrhythmic Drugs

Drug	PAP/PCWP	SVR	Contractility	SVI/CI	LVEF
Quinidine	0	↓	O or sl ↓	0	0
Procainamide	0	↓	O or sl ↓	0	0
Disopyramide	↑	↑	↓	↓	↓
Mexiletine	0	sl ↓	O or sl ↓	0	0
Tocainide	0	sl ↓	O or sl ↓	0	0
Moricizine	sl ↑	0	O or sl ↓	0	0
Encainide	0	↑	sl ↓	sl ↓	0
Flecainide	↑	↑	↓	↓	↓
Propafenone	↑	↑	↓	↓	sl ↓
Amiodarone	0	↓	O or sl ↓	0	0

CI = cardiac index; LVEF = left ventricular ejection fraction; O = no change; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; sl = slight; SVI = stroke volume index; SVR = systemic vascular resistance; ↓ = decrease; ↑ = increase.

tance and reduces afterload.[19] The occurrence of CHF is unusual. Crawford et al[20] evaluated the LV function of 10 normal subjects and 8 patients with congestive cardiomyopathy using M-mode echocardiography. No significant changes were observed in either group. These investigators concluded that any depressive effects on LV performance produced by long-term administration of oral quinidine in therapeutic doses are negligible. Furthermore, no exacerbation of CHF in patients receiving long-term quinidine therapy was noted in the Boston Collaborative Drug Surveillance Program,[21] even in patients with a history of CHF.

Tocainide: In animal studies, tocainide exerts minimal negative inotropic activity.[22] When given intravenously, there is a mild depressant effect in myocardial function, an increase in systemic vascular resistance or afterload and reduction in cardiac index.[23] Clinically oral tocainide is well tolerated by patients with normal LV function.[24] In a study by Klein et al,[25] oral tocainide did not cause worsening of CHF in patients after a myocardial infarction even when LVEF was <30%. In the report of Ravid et al,[17] tocainide induced failure in 1.6% of all patients, but in 3.7% of patients with a history of CHF.

Mexiletine: Intravenous mexiletine has been reported to reduce cardiac function, primarily in patients with a history of CHF.[26] However, the oral drug does not produce significant changes in LV function. In a study of 10 patients with a mean baseline EF of 28%, doses of mexiletine that were effective for suppression of arrhythmia did not alter LVEF.[27] In the study of Ravid et al,[17] the precipitation of failure by mexiletine in patients with a prior history of CHF was 2%. In a long-term study of oral mexiletine involving 107 patients, 46% of whom had CHF, only 1 patient developed cardiac decompensation during an average follow-up of 22.8 months.[28]

Encainide: Encainide has been reported to be hemodynamically well tolerated in patients with and without CHF.[29] However, when given intravenously, the drug does cause a dose-related depressant effect on myocardial function and an increase in systemic vascular resistance.[30] In contrast, DiBianco et al[31] reported that oral encainide, in doses effective for reducing ventricular ectopy, did not impair LV function at rest or during exercise as measured by radionuclide studies in any patient regardless of the baseline LVEF. In studies by Sami et al[29,30] involving patients with clinical CHF or a severely depressed radionuclide LVEF (averaging 22%), the oral drug did not produce a clinical worsening of CHF or reduction of LVEF. In contrast to these reports, a recent study by Gottlieb et al[32] involving 15 patients with clinical CHF reported significant adverse effects on invasively measured hemodynamics after a single 50-mg oral dose of encainide and 8 patients had a clinical worsening of CHF. In the study of Ravid et al,[17] almost 6% of patients with a history of CHF had exacerbation.

Procainamide: Information on the hemodynamic effects of procainamide is limited. Studies evaluating the hemodynamic effects of intravenous procainamide reported that the drug does reduce LV contractility and decreased cardiac output, especially in patients with preexisting LV compromise.[33–35] However, despite this statistically significant depression of myocardial function due to the intravenous drug, the oral preparation at recommended doses is well tolerated clinically and CHF exacerbation is rare. This conclusion is further supported by Burton et al,[36] who found no clinically significant deterioration in 15 patients with severe CHF treated with procainamide. Unfortunately, other data on the hemodynamic effects of oral procainamide are not available.

Disopyramide: Disopyramide can precipitate new CHF and cause exacerbation of preexisting myocardial dysfunction when given intravenously or orally. Early studies from Europe reported that when given intravenously in recommended doses, disopyramide exerted transient negative inotropic effect in patients with borderline or overt CHF with return to normal 10 minutes after the end of the infusion.[37] The adverse hemodynamic effects appeared to correlate with peak plasma drug levels. These results were confirmed by Leach et al[15] who studied 9 patients with LV dysfunction given intravenous bolus doses of disopyramide over 5- and 15-minute periods. Hemodynamic deterioration occurred immediately in all patients, whereas severe reduction in cardiac output occurred in 2 patients necessitating drug discontinuation. In the other 7 patients, the hemodynamic parameters returned to baseline levels by the end of the infusion. Podrid et al[16] reviewed the results of therapy in 100 patients receiving oral disopyramide. In those with a previous history of CHF, 55% had an exacerbation of CHF, whereas in patients without antecedent CHF the incidence was 5%. DiBianco et al[38] reviewed 12 studies of disopyramide in humans, and concluded that while acute intravenous administration of this drug causes significant negative inotropic effects, the oral form produces clinically insignificant adverse effects on myocardial performance in patients with normally functioning left ventricles. However, significant adverse hemodynamic consequences can occur in patients with clinical CHF.

Flecainide: Flecainide is a newer antiarrhythmic drug that has been shown to have significant negative inotropic effects, especially in patients with a previous history of CHF. Legrand et al[39] invasively measured the hemodynamic effects of intravenous flecainide in 10 patients free of overt CHF who were within 6 weeks of a myocardial infarction. Each patient had a significant decrease in EF (mean reduction 9%) within 15 minutes of beginning the infusion. These findings were confirmed by Josephson et al,[40] who reported a 16% reduction in LVEF when intravenous flecainide was given to 22 patients with coronary artery disease. Dunselman et al[14] infused the same dose of drug, but at a slower rate and observed a similar degree of myocardial depression. There are less data available on oral flecainide, but it has been reported that the oral drug may precipitate CHF in patients with a prior history of CHF.[40] The Flecainide-Quinidine Research Group[41] reported a worsening of CHF due to flecainide in only 2 of 141 patients (1.4%) with a prior history of mild CHF. In contrast, the Flecainide Ventricular Tachycardia Study Group[42] reported a 6% incidence of new or worsened CHF in patients taking oral flecainide.

Amiodarone: Amiodarone, a class III antiarrhythmic, has unique properties including an extremely long half-life and a heterogeneous distribution into different tissues. Chiale et al[43] reported that oral amiodarone did not provoke CHF in patients with a history of CHF. Cleland et al[44] reported similar results in 22 patients with CHF. No patient developed symptoms of CHF, and LVEF and cardiac index during treatment with placebo or amiodarone were similar. The same observations were reported by Haffajee et al[45] and Nademanee et al.[46] DePaola et al[47] assessed long-term oral amiodarone in 126 patients being treated for sustained VT. Baseline LVEF was 25% and one-third of the patients had a history of CHF. There was a small but significant increase in LVEF after 1 year of therapy. However, in 9 patients new CHF developed and in 7 CHF was exacerbated. Trobaugh et al[48] reported similar results in 70 patients treated for an average of 66 days with oral amiodarone. The mean LVEF increased from 40 to 43%, although in 7 patients there was a significant decrease in the LVEF. Clinically, 19% of patients experienced new or worsened CHF and this occurred more often in those with EF <35%.

Propafenone: Propafenone is a new agent that has a significant effect on LV function in patients with a history of CHF.[49] Studies of intravenous propafenone indicate that the drug has mild cardiac depressant effects when given at a dose of 2 mg/kg.[49] Podrid et al[50] reported that oral propafenone does not alter LV function in patients with baseline LVEF <50% or in the subgroup with <30%. Although the measured LVEF is not altered, CHF may nevertheless occur. In the study of Ravid et al,[17] 9% of patients with a history of CHF had exacerbation of CHF. Baker et al[51,52] also reported exacerbation of CHF with propafenone in patients with a history of CHF.

Hemodynamic effects of moricizine: In a review of several studies using noninvasive and invasive methods for evaluating LV function, Pratt et al[53] reported that moricizine did not alter any parameter. Among 81 patients who underwent 2-dimensional echocardiography before and during moricizine therapy, LVEF was 47 and 46%, respectively. No change was noted in those with LVEF <45% (31 vs 31%). LVEF was measured with radionuclide studies in 24 patients and was unchanged during moricizine therapy (40 vs 38%, difference not significant [NS]). In the subset of patients with LVEF <45% (average 27%) there was no change due to moricizine (25%, p = NS). Invasive hemodynamic measurements were obtained in 20 patients at rest and during bicycle ergometry. When compared with placebo, moricizine did not alter any measured parameter including heart rate, blood pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac index, stroke volume index or systemic vascular resistance.

Occurrence of congestive heart failure during moricizine therapy: Additional data regarding the safety of moricizine in patients with CHF are based on 1,072 patients receiving the drug as part of the trials performed in the United States. Of this group, 853 were men and 219 were women. The average age of the patients was 59 years (range 18 to 86). In each case, the indication for therapy with moricizine was the suppression of ventricular arrhythmia which included frequent VPCs only in 99 patients (9%), runs of nonsustained VT in 575 patients (54%) and a sustained ventricular tachyarrhythmia, including VT and ventricular fibrillation, in 398 patients (37%). A history of clinically manifest CHF was present in 467 patients (44%), whereas 605 did not have this finding. The diagnosis of CHF was made by the individual investigator, confirmed by review of medical records and was based on standard criteria including (1) the presence of symptoms (i.e., shortness of breath, exertional and paroxysmal nocturnal dyspnea and orthopnea); (2) physical findings including an enlarged heart, sinus tachycardia, a third heart sound, rales, neck vein distention, peripheral edema and hepatomegaly; (3) treatment consistent with CHF; and (4) confirmatory laboratory data including evidence of failure on chest x-ray or significant LV dysfunction determined by radionuclide scan or echocardiography.

TABLE III Relation Between Left Ventricular Function and Presenting Arrhythmia—Moricizine Data Base

	No. of Pts.	Percent with Arrhythmic Form		
		VPCs	NSVT	Sustained VT
No CHF	605	16	59	25*
Prior CHF	467	<1	47	53*
LVEF <30%	133	0	47	53
LVEF 30–45%	129	1	52	47
LVEF >45%	177	11	64	25

* p <0.01.
CHF = congestive heart failure; LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; VPC = ventricular premature complex; VT = ventricular tachyarrhythmia.

A global LVEF was determined by radionuclide or contrast ventriculography in 439 patients. LVEF was <30% in 133 patients (30% of 439), 30 to 45% in 129 patients (30%) and >45% in 177 (40%). In those with clinical CHF, LVEF was 34%, whereas in those without a history of CHF it was 52% (p <0.01). A history of a sustained ventricular tachyarrhythmia was seen more often among patients with a history of CHF (p <0.01) as well as those with LVEF <30% (Table III).

During the course of therapy with moricizine, CHF occurred in 7.1% of patients (76 of 1,072) (Table IV).

TABLE IV Development of Congestive Heart Failure (CHF) with Moricizine

	% Patients Developing CHF	
Total population (n = 1,072)	7.1	
Prior CHF (n = 467)	15.4	
No prior CHF (n = 605)	0.8	
Dose (mg/day)		
<600	5.2	
600	8.2	
750	5.6	p = NS
900	6.6	
>900	2.4	

NS = not significant.

TABLE V Relation Between Incidence of Adverse Reactions and History of Congestive Heart Failure (CHF)

Adverse Reactions	Incidence of Adverse Effects (%) Prior CHF (n = 467 pts.)	No Prior CHF (n = 605 pts.)	p
Cardiovascular*	19	15	NS
Neurologic	14	13	NS
Gastrointestinal	11	9	NS
Systemic	6	7	NS
Special senses	3	3	NS
Pulmonary	5	2	0.001
Dermatologic	3	2	NS
Genitourinary	1	2	NS
Metabolic	1	1	NS
Musculoskeletal	<1	1	NS
Hematologic	<1	<1	NS

* Conduction abnormalities, hypotension and arrhythmia aggravation were more frequent in patients with CHF.
NS = not significant.

CHF was judged to be definitely related to moricizine therapy in 12 patients (1%), whereas in 12 patients (1%) it was possibly due to drug. The average daily dose of the drug was equivalent in those in whom CHF developed (865 mg) compared with those in whom this complication did not develop (869 mg, p = NS). Of the 467 patients with a history of CHF, 15% had a worsening of CHF. In contrast, only 5 of 605 patients (0.8%) without previous CHF developed this complication. The average LVEF was 34% in the group of patients with a history of CHF, whereas it was 25% in the subjects who developed a worsening of CHF.

CHF occurred in 53% within 2 weeks and within 3 months in 69% of these patients. All but 2 patients developed this complication within the first year. There was no relation between the daily dose of moricizine and the development of congestive failure. The incidence of CHF was 5.2, 8.2, 5.6, 6.6 and 2.4% in those receiving <600, 600, 750, 900 and >900 mg, respectively (p = NS). Of the 76 patients in whom CHF developed during moricizine therapy, 43% discontinued taking the drug, whereas the remaining patients were treated medically and continued to receive therapy.

TABLE VI Relation Between Incidence of Adverse Reactions and Left Ventricular Ejection Fraction (LVEF)

	Incidence of Adverse Effects (%) LVEF <30% (n = 133 pts.)	LVEF 30–45% (n = 129 pts.)	LVEF >45% (n = 177 pts.)
Cardiovascular	22	19	14
Neurologic	14	18	16
Gastrointestinal	13	10	8
Systemic	8	6	5
Special senses	2	0	5
Pulmonary	8	2	2
Dermatologic	4	2	1
Genitourinary	1	2	1
Metabolic	1	2	2
Musculoskeletal	0	0	1
Hematologic	0	0	0

p = NS for all values.

Moricizine was also administered to 98 patients with a recent myocardial infarction as part of the Cardiac Arrhythmia Pilot Study (CAPS). A history of CHF was present in 23 patients, but worsening of CHF did not occur in any patient during drug therapy. None of the 75 patients without a history of CHF developed this complication.

In conclusion, the precipitation of CHF during moricizine therapy is uncommon and occurs primarily in patients with a prior history of CHF and a low LVEF.

RELATION BETWEEN ADVERSE EFFECTS FROM ANTIARRHYTHMIC DRUGS AND LEFT VENTRICULAR FUNCTION

Whereas it might be expected that adverse effects from antiarrhythmic drugs would occur more often in patients with CHF, data are sparse. Most of the previous studies reporting the results of therapy with antiarrhythmic drugs do not address this issue. However, it has been reported that the provocation of CHF is seen more often in patients with a history of CHF.[17,18] A similar relation has been reported with aggravation of arrhythmia.[54]

All antiarrhythmic drugs can cause arrhythmia aggravation and this is one of the most serious adverse effects associated with this class of drug. Velebit et al[55] retrospectively reviewed 722 antiarrhythmic drug tests involving 155 patients and reported an 11.1% incidence of arrhythmia aggravation. In this study, it did not appear that the degree of cardiac dysfunction before testing was predictive of this complication. However, in a recent update of this complication, Slater et al[54] observed that the presence of a reduced LVEF <35% and a clinical history of CHF was predictive of arrhythmia aggravation (p = 0.04). Morganroth and Horowitz[56] also reported that the incidence of arrhythmia aggravation was higher in patients with LV dysfunction. In the recent study by Pratt et al,[18] similar data were reported. The average LVEF was 30% in those who had arrhythmia aggravation compared with 45% in drug responders (p <0.0001). Among the 101 patients with LVEF <40%, 13 had arrhythmia aggravation. In contrast, this complication occurred in only 8 of 145 patients (5.5%) with LVEF >40%. The relation between other drug-related adverse effects and LV function have not been reported.

Relation between left ventricular function and adverse effects from moricizine: The data base of 1,072 patients receiving moricizine was analyzed in order to establish a relation between CHF (Table V) and LVEF (Table VI) and the incidence of adverse effects with this agent.

Cardiovascular: A cardiovascular adverse reaction occurred in 177 patients (16.5%), of whom 88 (18.8%) had a history of CHF while 89 patients (14.7%) did not have failure. There was no significant difference in the frequency of any cardiovascular adverse effect between those with and without failure. The only exceptions were an intraventricular conduction delay which occurred more often in patients with CHF (4.1 vs 1.8, p = 0.04) and hypotension, and also more frequently in patients with CHF (1.7 vs 0.03%, p = 0.04). As with other agents,

arrhythmia aggravation due to moricizine was also more common in patients with a history of CHF. Of the 467 patients with clinical CHF, 35 (7.5%) had arrhythmia aggravation within 14 days of the initiation of therapy, 11 (2.4%) of whom died suddenly. In contrast, arrhythmia aggravation occurred in only 15 of 605 patients (2.5%) who did not have CHF and only 2 patients (0.3%) died suddenly ($p = 0.002$).

When analyzed by LVEF, 21.8% of patients with <30% EF had a cardiovascular side effect, 19% with an EF 30 to 45% had a cardiovascular adverse reaction and 14% with >45% reported a cardiovascular side effect. The incidence of each type of adverse reaction was equivalent in all 3 groups.

Nervous system: An adverse reaction involving the central nervous system occurred in 14% of patients with and 13% without CHF (p = NS). There was no significant difference in the frequency of any neurologic adverse reaction between those with and without CHF. When analyzed by LVEF the incidence of any neurologic complaint was similar in 3 subgroups (14 vs 18 vs 16%, p = NS).

Gastrointestinal: An adverse reaction involving the gastrointestinal system was reported by 11% of those with CHF and 9% among patients without CHF (p = NS). The incidence of each gastrointestinal side effect was the same in those with and without CHF. Nausea was more frequent in those with CHF (7 vs 4%), but this was not statistically different. Gastrointestinal side effects tended to be more frequent in patients with an LVEF <30% (13%) than in those with 30 to 45% (10%) and in those with an EF >45% (8%), but this did not reach statistical significance. This was primarily due to a greater incidence of nausea among these patients (8 vs 3 vs 5%).

Respiratory system: Adverse reactions involving the respiratory system were more frequent in those with CHF (5 vs 1%, $p = 0.001$), primarily related to a greater incidence of dyspnea and pulmonary congestion in those with a history of CHF. All other pulmonary complaints were of equal frequency in those with and without CHF. As expected, adverse pulmonary reactions occurred more often in the group with the lowest LVEF (8 vs 2%), primarily because of an increased frequency of dyspnea and pulmonary congestion in this group.

Other systems: There was no significant difference in the incidence of adverse reactions, which were infrequent, involving the dermatologic, urologic, musculoskeletal, endocrine, hematopoietic or ophthalmologic systems in those with and without CHF. Similarly, there was no relation to LVEF.

RELATION BETWEEN DRUG EFFICACY AND CONGESTIVE HEART FAILURE

When assessing the efficacy of a drug in patients with CHF, important factors to consider include the characteristics of the patient population in whom the drug is given, as well as the criteria used for determining efficacy. Patients differ from one study to another and even within a study with regard to etiology of the heart disease, symptomatology, NYHA class, symptomatic vs asymptomatic arrhythmia, LVEF, etiology of CHF and presence of comorbid conditions. Such variability has obvious implications for the application of study results to patients in clinical practice. Another problem relates to the definition of efficacy used by various studies which include the degree of arrhythmia suppression, the prevention of sustained arrhythmia or the prevention of sudden death and reduction in mortality.

Some investigators have chosen the abolition of ventricular arrhythmia documented either invasively by electrophysiologic testing or noninvasively by ambulatory monitoring as an end point for defining drug effectiveness. However, the percentage of ventricular arrhythmia suppression necessary is uncertain and it is unclear how reliably suppression correlates with prevention of sudden cardiac death, especially in patients with LV dysfunction. Graboys et al[57] reported that the suppression of nonsustained VT on monitor and exercise testing predicted improved survival in a subset of patients with a history of a hemodynamically significant sustained ventricular tachyarrhythmia and LV dysfunction. However, there are no data to suggest that arrhythmia suppression based on noninvasive techniques will prevent a sustained ventricular tachyarrhythmia in patients with CHF who have asymptomatic arrhythmia. Furthermore, studies evaluating patients with an idiopathic dilated cardiomyopathy and CHF who have had a hemodynamically significant ventricular tachyarrhythmia have reported that noninducibility of arrhythmia during electrophysiologic testing while taking antiarrhythmic drugs does not always predict freedom from recurrence.[58,59] This remains controversial, however, because other studies[60] involving patients with idiopathic dilated cardiomyopathy have reported that noninducibility with electrophysiologic testing during antiarrhythmic therapy is predictive of a good prognosis. However, only a small number of such patients with a cardiomyopathy are rendered noninducible.

Brodsky et al[61] studied 20 patients with CHF and symptomatic ventricular arrhythmia. Patients were treated with single or combination antiarrhythmic drug therapy, the second drug being a β blocker in 55%. One-year survival was 89%, which compared favorably to the expected 40 to 60% survival in this patient population. However, these results may be confounded by the use of β blockers, making an assessment of the independent effect of antiarrhythmic therapy difficult to evaluate. In a 2-phase study by Cleland and Dargie,[62] 62 patients with CHF underwent exercise testing and those in whom VT developed had a significantly reduced 2-year survival (22%) than the group without arrhythmia (55%). Twenty-two patients entered a placebo-controlled, crossover trial with amiodarone. This drug effectively suppressed exercise-induced ventricular arrhythmia, but survival was not reported.

In a nonrandomized study, Chakko and Gheorghiade[5] evaluated 43 patients with CHF and asymptomatic ventricular arrhythmia, 23 of whom were treated with a type 1A antiarrhythmic agent, whereas 22 did not receive an antiarrhythmic drug. After a 16-month follow-up, overall

TABLE VII Relation Between History of Congestive Heart Failure (CHF), Presenting Arrhythmia and Arrhythmia Suppression

	Prior CHF (n = 164 pts.)	No Prior CHF (n = 360 pts.)
Age (yrs)	60*	57*
% patients with:		
VPCs	1*	14*
NSVT	74	71
Sustained arrhythmia	26*	15*
LVEF (%)	34*	52*
% responders†	57‡	55‡
% VPC suppression	85‡	88‡
% with NSVT elimination	54‡	64‡

* p <0.01.
† Criterion for response is >75% reduction in VPCs.
‡ p = NS.
Abbreviations as in Tables III and IV.

mortality and sudden cardiac death were equivalent in the 2 groups, but in this study there was no attempt to suppress arrhythmia. Parmley and Chatterjee[4] reported on 78 patients with severe CHF, of whom 39 patients were treated with a type 1A antiarrhythmic or amiodarone. After a 6-month follow-up, sudden death mortality was reduced when compared with patients not taking antiarrhythmic therapy. However, this was not a randomized trial and therapy was not guided by arrhythmia suppression.

A weakness of each of these trials is that they are not controlled. Further studies randomizing patients with CHF to suppressive therapy or placebo are needed before firm conclusions regarding antiarrhythmic drug use in such patients can be made.

There have been several reports that antiarrhythmic drugs are more effective in patients with preserved LV function. In a retrospective review of 94 patients with a sustained ventricular tachyarrhythmia, Hohnloser et al[63] reported that the overall efficacy rate of antiarrhythmic drugs was significantly lower in patients with reduced LVEF. In those with LVEF <35%, drugs tested were effective in only 34% of studies compared with a 46% efficacy rate in those with LVEF >35% (p = 0.03). LVEF was an independent predictor of drug efficacy and was significantly lower in patients who did not respond to drugs (29 vs 42% in responders, p = 0.017). Additionally, LVEF was an independent predictor of long-term outcome. LVEF was 31% in patients with arrhythmia recurrence compared with 44% in patients who remained free of arrhythmia during follow-up. Of 49 patients with an EF >35%, there were 2 sudden deaths and 6 nonfatal recurrences. In contrast, there were 7 sudden deaths and 13 recurrences among the 45 patients with LVEF <35% (p = 0.003). In a larger group of 161 patients with coronary artery disease, Lampert et al[64] reported that the average LVEF in patients who responded to antiarrhythmic drugs was 40% compared with 32% in nonresponders (p <0.05). Additionally, a clinical history of CHF was more frequent in nonresponders than in drug responders (55 vs 36%, p = 0.017) as was cardiomegaly on chest x-ray (63 vs 38%, p = 0.002). Independent predictors of arrhythmia recurrence included a clinical history of CHF (p = 0.0009), evidence of CHF on physical examination (rales, S_3) (p <0.05) and LVEF (p <0.002).

In the recent study of Pratt et al,[18] responders to drugs had a significantly greater LVEF (39 vs 26%) (p = 0.04). Of the 101 patients with LVEF <40%, arrhythmia suppression occurred in 26% compared with 39% of those who had an EF >40%. Nonsustained VT was present in 132 patients and these forms were suppressed in 67% of those with an EF >40%, compared with suppression in only 47% of those with an EF <40% (p = 0.03). When LVEF >30% or <30% was considered, suppression was achieved in 67 vs 36%, respectively (p = 0.0008).

In several studies involving individual drugs, a similar relation between response to drug and LV function had been reported. Tordjman et al[65] reported on 102 patients receiving encainide. The response rate was 50% in patients with LVEF >35% while only 29% of those with LVEF <35% responded. In a study of tocainide therapy, Hohnloser et al[66] reported that LVEF was significantly greater in responders than nonresponders (43 vs 37%).

TABLE VIII Relation Between Left Ventricular Function, Moricizine Dose and Arrhythmia Suppression

	Dose (mg/day)			
	600	750	900	>900
	% VPC Suppression			
LVEF <30%	82	79	81	73
LVEF 30–45%	94	84	87	90
LVEF >45%	95	91	92	93
Prior CHF	81	85	88	88
No prior CHF	87	92	88	91
	% Responders*			
LVEF <30%	44	50	55	33
LVEF 30–45%	57	44	65	36
LVEF >45%	64	48	68	71
Prior CHF	59	58	65	57
No prior CHF	51	57	59	56

* Criterion for response is >75% decrease in VPCs.
p = NS for all groups.
CHF = Congestive heart failure; other abbreviations as in Tables III and IV.

Relation between left ventricular function and efficacy of moricizine: Adequate ambulatory monitoring (≥18 hours) at baseline was obtained in 524 patients, of whom 164 had and 360 did not have a history of CHF. Drug efficacy, defined as ≥75% suppression of VPCs, was achieved in 57% of patients with a history of CHF and in 55% of patients without CHF (p = NS) (Table VII). Mean VPC suppression was 85% in patients with compared to 88% in those without CHF (p = NS). Complete elimination of runs of nonsustained VT was achieved in 54% of patients with CHF, whereas abolition of runs was achieved in 64% of those without failure. Moreover, the percentage of patients responding to moricizine and the mean percentage of VPC suppression in patients with and without CHF were equivalent to all doses more than 600 mg/day (Table VIII).

Of the 220 patients with adequate ambulatory monitoring data who had measurement of LV function, LVEF

was <30% (mean 21%) in 46 patients, 30 to 45% (mean 38%) in 57 patients and >45% (mean 59%) in 117 patients (Table IX). A clinical history of CHF was present in 76, 42 and 18% of patients, respectively, in the 3 groups. Drug efficacy was achieved in 50% of patients with LVEF <30%, in 51% of patients with LVEF 30 to 45%, and in 59% of those with LVEF >45% (p = NS). Mean reduction in VPCs in the 3 subgroups was 80, 88 and 91%, respectively (p = NS). Similarly, the number of patients with complete abolition of runs of nonsustained VT was equivalent in the 3 subgroups: 49, 54 and 63%, respectively (p = NS). The percentage of patients responding to moricizine and the mean percent of VPC suppression were equivalent at each dose level within each subgroup of patients (Table VIII).

In addition, ambulatory monitoring data are available for all patients (n = 98) entered into CAPS. The criterion for efficacy in this study was ≥70% reduction of VPCs and >90% reduction of runs of nonsustained VT. Of the 23 patients with clinical CHF, 16 (70%) responded to moricizine, whereas 66% (49 of 75) without CHF responded (p = NS). Of the patients in the study, 22 had LVEF <30%, of whom 12 (55%) responded to moricizine. Among the 25 with LVEF of 30 to 45%, 16 patients (64%) responded, whereas 73% (37/51) of those with an EF >45% responded. Although there was a trend for a higher response rate when LVEF was greater, these differences were not significant.

In studies involving only patients with a history of refractory sustained ventricular tachyarrhythmias, moricizine is more effective in patients with better LV function. Pratt et al[67] reported on 50 patients with serious ventricular arrhythmia who were treated with moricizine. Discontinuation of the drug because of inefficacy was more frequent in patients with a lower LVEF. Thus, 61% of patients with LVEF >30% responded to the drug compared with 22% response rate in those with LVEF <30% (p <0.04). The average LVEF was lower in nonresponders than in responders (32 vs 42%, p <0.01). In a report by Hession et al[68] involving 102 patients with malignant ventricular arrhythmias managed noninvasively, 35% of patients with LVEF >40% (mean 58%) responded to the drug compared with an 18% response rate in those with LVEF <40% (mean 25%) (p <0.05). The average LVEF was 46% in responders compared with 39% in nonresponders (p <0.05).

TABLE IX Relation Between Left Ventricular Ejection Fraction (LVEF), Presenting Arrhythmia and Arrhythmia Suppression

	Baseline LVEF (%)		
	<30 (n = 46 pts.)	30–45 (n = 57 pts.)	>45 (n = 117 pts.)
History of CHF (%)	76	42	18
% patients with			
VPCs	0	2	14
NSVT	67	68	72
Sustained arrhythmia	33	30	14
% responders*	50†	51†	59†
% VPC suppression	80†	88†	91†
% patients with NSVT elimination	49†	54†	63†

* Criterion for efficacy is >75% decrease in VPCs.
† p = NS.
Abbreviations as in Tables III and IV.

CONCLUSION

Patients with CHF have a poorer response to antiarrhythmic drugs and are more likely to experience serious toxic side effects, particularly aggravation of arrhythmia and exacerbation of CHF, than patients without CHF. However, unlike other drugs, moricizine appears to be equally effective in patients with frequent ventricular arrhythmia irrespective of LV function or history of CHF. However, in patients presenting with serious sustained ventricular tachyarrhythmias, moricizine is less effective when LVEF is reduced and CHF is present. Like other agents, arrhythmia aggravation and exacerbation of CHF are more frequent in patients with a history of CHF and a reduced LVEF. However, the frequency of other adverse effects caused by moricizine is unassociated with the state of LV function. Moricizine appears to be as well tolerated in patients with CHF as in those with intact LV function.

REFERENCES

1. Parmley WW. Factors causing arrhythmia in chronic congestive heart failure. *Am Heart J 1987;114:1267–1272.*

2. Francis GS, Chatterjee K, Prystowsky EN. Should asymptomatic ventricular arrhythmias in patients with congestive heart failure be treated with antiarrhythmic drugs? *JACC 1988;12:274–283.*

3. Wilson JR. Use of antiarrhythmic drugs in patients with heart failure: clinical efficacy, hemodynamic results, and relation to survival. *Circulation 1987;75:suppl IV:IV-64–IV-73.*

4. Parmley WW, Chatterjee K. Congestive heart failure and arrhythmias: an overview. *Am J Cardiol 1986;57:34B.*

5. Chakko CS, Gheorghiade M. Ventricular arrhythmias in severe heart failure: incidence, significance, and effectiveness of antiarrhythmic therapy. *Am Heart J 1985;109:497–504.*

6. Huang SK, Messer JV, Denes P. Significance of ventricular tachycardia in idiopathic dilated cardiomyopathy: observations in 35 patients. *Am J Cardiol 1983;51:507–512.*

7. Woosley RL. Pharmacokinetics and pharmacodynamics of antiarrhythmic agents in patients with congestive heart failure. *Am Heart J 1987;114:1280–1291.*

8. Siddoway LA. Initial dosage selection of antiarrhythmic therapy. *Am J Cardiol 1988;6L:2H–8H.*

9. Crouthamel WG. The effect of congestive heart failure on quinidine pharmacokinetics. *Am Heart J 1975;90:335–339.*

10. Kessler KM, Kayden DS, Estes DM, Koslovskis PL, Sequeira R, Trohman RG, Palomo AR, Myerburg RJ. Procainamide pharmacokinetics in patients with acute myocardial infarction or congestive heart failure. *JACC 1986;7:1131–1139.*

11. Angelakos E, Hastings E. The influence of quinidine and procainamide on myocardial contractility in vivo. *Am J Cardiol 1960;5:791–798.*

12. Chiba S. Effects of quinidine, procainamide, lidocaine and phenytoin on inotropic responses to acetylcholine and norepinephrine. *Jpn J Pharmacol 1976;26:276–278.*

13. Nelson LD, Schmid PG, Holmsten D, Mark AL, Heistad DD, Abboud FM. Effects of quinidine on venous responses to adrenergic and nonadrenergic constrictor stimuli: indirect evidence of two sites of action in vascular smooth muscle. *Proc Soc Exp Biol Med 1974;146:409–413.*

14. Dunselman PHJM, Kingma JH, van Wijk LM, Disk A, Wesseling H, Lie KI. Hemodynamic and antiarrhythmic effects of intravenous flecainide acetate in chronic congestive heart failure. *Drugs 1985;suppl 4:58–64.*

15. Leach AJ, Brown JE, Armstrong PW. Cardiac depression by intravenous disopyramide in patients with left ventricular dysfunction. *Am J Med 1980; 68:839–844.*

16. Podrid PJ, Schoeneberger A, Lown B. Congestive heart failure caused by oral disopyramide. *N Engl J Med 1980;302:614–617.*

17. Ravid S, Podrid PJ, Lampert S, Lown B. Congestive heart failure induced by 6 of the new antiarrhythmic drugs. *JACC 1989;14:1326–1330.*

18. Pratt LM, Eaton T, Francis M, Woolbert S, Muhmarian J, Roberts R, Young JB. The inverse relationship between baseline left ventricular ejection

fraction and outcome of antiarrhythmic therapy: A dangerous imbalance in the risk benefit ratio. *Am Heart J 1989;118:433–440.*

19. Ferrer MI, Harvey M, Weaks L, Drisdale DT, Cournand A, Richards DW. Some effects of quinidine sulfate on the heart and circulation in man. *Am Heart J 1988;36:816–837.*

20. Crawford MH, White DH, O'Rourke RA, Amon KW. Effects of oral quinidine on left ventricular performance in normal subjects and patients with congestive cardiomyopathy. *Am J Cardiol 1979;44:714–718.*

21. Cohen IS, Hershel J, Cohen SI. Adverse reactions to quinidine in hospitalized patients: Findings based on data from the Boston Collaborative Drug Surveillance Program. *Prog Cardiovascular Dis 1977;20:151–163.*

22. Coltart DJ, Berndt TB, Ternoff R, Harrison DC. Antiarrhythmic circulatory effects of Astra W3609J: A new lidocaine like agent. *Am J Cardiol 1974;34:35–41.*

23. Winkle RA, Anderson JL, Peter F, Meffin PJ, Fowles RE, Harrison DC. The hemodynamic effects of intravenous tocainide in patients with heart disease. *Circulation 1978;57:787–792.*

24. Young MD, Hadidian Z, Horn HR, Johnson JL, Vassallo HG. Treatment of ventricular arrhythmias with oral tocainide. *Am Heart J 1980;100:1041–1047.*

25. Klein MMD, Levine PA, Ryan TJ. Antiarrhythmic efficacy, pharmacokinetics and clinical safety of tocainide in convalescent myocardial infarction patients. *Chest 1980;77:726–730.*

26. Saunamaki KI. Hemodynamic effects of a new anti-arrhythmic agent, mexiletine (Ko 1173) in ischemic heart disease. *Cardiovasc Res 1975;9:788–792.*

27. Stein J, Podrid PJ, Lown B. Effects of oral mexilitine on left and right ventricular function. *Am J Cardiol 1984;54:575–578.*

28. Stein J, Podrid PJ, Lampert S, Hirsowitz G, Lown B. Long-term mexilitine for ventricular arrhythmia. *Am Heart J 1984;107:1091–1098.*

29. Sami MH, Derbekyan VA, Lisbona R. Hemodynamic effects of encainide in patients with ventricular arrhythmia and poor ventricular function. *Am J Cardiol 1983;52:507–511.*

30. Sami MH. Acute intravenous and long-term oral hemodynamic effects of encainide. *Am J Cardiol 1986;58:25C–30C.*

31. DiBianco R, Fletcher RD, Cohen AI, Gottdiener JS, Singh SN, Katz RJ, Bates HR, Sauerbrunn B. Treatment of frequent ventricular arrhythmia with encainide: assessment using serial ambulatory electrocardiograms, intracardiac electrophysiologic studies, treadmill exercise tests and radionuclide cineangiographic studies. *Circulation 1982;65:1134–1147.*

32. Gottlieb SS, Kukin ML, Yushak M, Medina N, Packer M. Adverse hemodynamic and clinical effects of encainide in severe chronic heart failure. *Ann Intern Med 1989;110:505–509.*

33. McClendon RL, Hansen WR, Kinsman JM. Hemodynamic changes following procainamide administration intravenously. *Am J Med Sci 1951;222:375–381.*

34. Jawad-Kanber G, Sherrod TR. Effect of loading dose of procainamide on left ventricular performance in man. *Chest 1974;66:269–272.*

35. Miller RR, Hilliard G, Lies JE, Massumi RA, Zelis R, Mason DT, Amsterdam EA. Hemodynamic effects of procainamide in patients with acute myocardial infarction and comparison with lidocaine. *Am J Med 1973;55:161–168.*

36. Burton JR, Matthew MT, Armstrong PW. Comparative effects of lidocaine and procainamide on acutely impaired hemodynamics. *Am J Med 1976;61:215–220.*

37. Jensen G, Sigurd B, Uhrenholt A. Hemodynamic effects of intravenous disopyramide in heart failure. *Eur J Clin Pharmacol 1975;8:167–173.*

38. DiBianco R, Gottdiener JS, Singh SN, Fletcher RD. A review of the effects of disopyramide phosphate on left ventricular function and the peripheral circulation. *Angiology 1987;38:174–183.*

39. Legrand V, Vandormael M, Collignon P, Kulbertus HE. Hemodynamic effects of a new antiarrhythmic agent, flecainide (R-818), in coronary heart disease. *Am J Cardiol 1983;51:422–426.*

40. Josephson MA, Kaul S, Hopkins J, Kvam D, Singh B. Hemodynamic effects of intravenous flecainide relative to the level of ventricular function in patients with coronary artery disease. *Am Heart J 1985;109:41–45.*

41. The Flecainide-Quinidine Research Group. Flecainide versus quinidine for treatment of chronic ventricular arrhythmias. *Circulation 1983;67:1117–1123.*

42. Flecainide Ventricular Tachycardia Study Group. Treatment of resistant ventricular tachycardia with flecainide acetate. *Am J Cardiol 1986;57:1299–1304.*

43. Chiale PA, Halpern MS, Nau GJ, Tambussi AM, Przybylski J, Lazzari JO, Elizari MV, Rosenbaum MB. Efficacy of amiodarone during long-term treatment of malignant ventricular arrhythmias in patients with chronic chagasic myocarditis. *Am Heart J 1984;107:656–665.*

44. Cleland JGF, Dargie HJ, Findlay IN, Wilson JT. Clinical, hemodynamic and antiarrhythmic effects of long-term treatment with amiodarone of patients in heart failure. *Br Heart J 1987;57:436–445.*

45. Haffajee CI, Love JC, Alepert JS, Asdourian GF, Sloan KL. Efficacy and safety of long-term amiodarone in treatment of cardiac arrhythmias: Dosage experience. *Am Heart J 1983;106:435–443.*

46. Nademanee K, Hendrickson JA, Cannom DS, Goldreyer BN, Singh BN. Control of refractory life-threatening ventricular tachyarrhythmias by amiodarone. *Am Heart J 1981;101:759–768.*

47. DePaola AAV, Horowitz LN, Spielman SR, Brady P, Morganroth J, Greenspan AM, Kay HR. Development of congestive heart failure and alterations in left ventricular function in patients with sustained ventricular tachyarrhythmias treated with amiodarone. *Am J Cardiol 1987;60:276–280.*

48. Trobaugh GB, Kudenchuk PJ, Greene HL, Tutt RC, Kingston E, Gorham JR, Gross BW, Graham EL, Sears GK, Werner JA. Effect of amiodarone on ventricular function as measured by gated radionuclide angiography. *Am J Cardiol 1984;54:1263–1266.*

49. Harron DWG, Brogden RN. Propafenone: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in the treatment of arrhythmias. *Drugs 1987;34:617–647.*

50. Podrid PJ, Cytryn R, Lown B. Propafenone: noninvasive evaluation of efficacy. *Am J Cardiol 1984;54:53D–59D.*

51. Baker BJ, Brodsky MA, Diah H, Allen BJ, Cotter B, Luckett C, Murphy ML. Hemodynamic effect of propafenone and the experience in patients with congestive heart failure. *J Electrophysiol 1987;1:527–535.*

52. Baker BJ, Dinh H, Kroskey D, deSoyza NDB, Murphy ML, Franciosa JA. Effect of propafenone on left ventricular ejection fraction. *Am J Cardiol 1984;54:20D–25D.*

53. Pratt CM, Podrid PJ, Seals AA, Young JB, Hession M, Lampert S, Quinones M, Lown B. Effects of ethmozine (moricizine HCl) on ventricular function using echocardiographic, hemodynamic and radionuclide assessment. *Am J Cardiol 1987;60:73F–78F.*

54. Slater W, Lampert S, Podrid PJ, Lown B. Clinical predictors of arrhythmia worsening by antiarrhythmic drugs. *Am J Cardiol 1988;61:349–353.*

55. Velebit V, Podrid PJ, Lown B, Cohen BH, Graboys TB. Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs. *Circulation 1982;65:886–894.*

56. Morganroth J, Horowitz LN. Flecainide: its proarrhythmic effects and expected changes on the surface electrocardiogram. *Am J Cardiol 1984;53:89B–94B.*

57. Graboys TB, Lown B, Podrid PJ, DeSilva R. Long-term survival of patients with malignant ventricular arrhythmia treated with antiarrhythmic drugs. *Am J Cardiol 1982;50:437–443.*

58. Magiros E, Platia E, Guarnieri T, Reid P, Grunwald L, Broomfield D, Griffith L. Failure of EP testing to predict death in congestive cardiomyopathy (abstr). *Circulation 1985;72:III:III-159.*

59. Milner PG, Lerman BB, Dimarco JP. Role of electrophysiologic testing in patients with idiopathic dilated cardiomyopathy and ventricular tachyarrhythmias (abstr). *Circulation 1985;72:III:III-159.*

60. Poll DS, Marchlinski FE, Buxton AE, Josephson ME. Usefulness of programmed stimulation in idiopathic dilated cardiomyopathy. *Am J Cardiol 1986;58:992–997.*

61. Brodsky MA, Allen BJ, Baron D, Chesnie BM, Abate D, Thomas R, Henry WL. Enhanced survival in patients with heart failure and life-threatening ventricular tachyarrhythmias. *Am Heart J 1986;112:1166–1172.*

62. Cleland JGF, Dargie HJ. Ventricular arrhythmias during exercise in patients with heart failure: the effect of amiodarone. *Eur Heart J 1987;8:suppl D:65–69.*

63. Hohnloser SH, Raeder EA, Podrid PJ, Graboys TB, Lown B. Predictors of antiarrhythmic drug efficacy in patients with malignant ventricular tachyarrhythmias. *Am Heart J 1983;114:1–7.*

64. Lampert S, Lown B, Graboys TB, Podrid PJ, Platt CM. Determinants of survival in patients with malignant ventricular arrhythmia. *Am J Cardiol 1988;61:791–797.*

65. Tordjman T, Podrid PJ, Raeder E, Lown B. Safety and efficacy of encainide for malignant ventricular arrhythmias. *Am J Cardiol 1986;58:87C–95C.*

66. Hohnloser SJ, Lang HW, Raeder EA, Podrid PJ, Lown B. Short and long term tocainide therapy for malignant ventricular tachyarrhythmias. *Circulation 1986;75:143–149.*

67. Pratt CM, Wierman A, Seals A, English L, Leon L, Young JB, Quinonis MA, Roberts L. Efficacy and safety of moricizine in patients with malignant ventricular tachycardia: results of a placebo-controlled prospective long term trial. *Circulation 1986;73:718–726.*

68. Hession M, Lampert S, Podrid PJ, Lown B. Ethmozine therapy in patients with complex arrhythmia. *Am J Cardiol 1987;60:59F–66F.*

Placement of Moricizine in the Selection of Antiarrhythmic Drug Therapy

Joel Morganroth, MD

The selection of antiarrhythmic drug therapy requires a careful assessment of the benefits of ventricular arrhythmia suppression compared with the risks of antiarrhythmic drug use. Since reduction in sudden cardiac death from ventricular arrhythmia suppression has not been demonstrated, the only indications for antiarrhythmic drug suppression involve the reduction of hemodynamic symptoms such as syncope (a major benefit) or the reduction of nonhemodynamic symptoms such as palpitations or dizziness (a minor benefit). Noncardiac adverse effects and organ toxicity as well as cardiac side effects must be considered when antiarrhythmic drug therapy is initiated. For reduction of nonhemodynamically important symptoms in patients with benign or potentially lethal ventricular arrhythmias, β blockers are chosen as first-line therapy. Because of moricizine's relatively high effectiveness in suppressing ventricular arrhythmias and its low potential for noncardiac adverse effects and organ toxicity as well as a low incidence of induced proarrhythmia and heart failure, moricizine is selected as the next drug in line. All other class I antiarrhythmic drugs either have been shown to have the potential for increasing sudden cardiac death or have major rates of noncardiac adverse effects or organ toxicity that preclude their use in these patient groups except in special circumstances. In patients with malignant ventricular arrhythmias who present with hemodynamic consequences such as syncope or worse, moricizine also is preferred as an initial drug for consideration. When compared to drugs with class IA and IB action, moricizine has comparable efficacy yet lower rates of noncardiac adverse effects, organ toxicity, proarrhythmia and heart failure. After moricizine, the therapy of choice would be quinidine or procainamide or a combination of drugs with class IA and IB action followed by drugs with class IC action and then amiodarone. Because of patient heterogeneity, careful analysis of the actual risk vs benefit of antiarrhythmic drug therapy must be considered for each individual patient. This algorithm should only be considered a general guideline requiring careful consideration for individual patient use.

(Am J Cardiol 1990;65:65D–67D)

From the Departments of Medicine & Cardiovascular Diseases, The Graduate Hospital and the University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19146.

Address for reprints: Joel Morganroth, MD, Center of Excellence for Cardiovascular Studies, The Graduate Hospital, One Graduate Plaza, Philadelphia, Pennsylvania 19146.

Before considering recommendations for differential selection of antiarrhythmic agents in the treatment of ventricular arrhythmias, it is important to remember that the decision to administer such therapy principally rests on the physicians assessment of its risk vs benefit ratio. Table I details the potential risks and benefits that should be considered during this clinical decision-making process. Whereas prevention of sudden cardiac death is the principal benefit sought by physicians in their treatment of patients with high-risk ventricular arrhythmias, only antiarrhythmic agents with class II action (β blockers) have shown that such a benefit is possible.[1] In fact, the Cardiac Arrhythmia Suppression Trial (CAST) has demonstrated that reduction of ventricular premature complexes, at least by drugs with class IC action[2] such as encainide and flecainide, have been associated with an enhanced rate of sudden cardiac death rather than the reverse.[3] Until further drug-specific mortality trials demonstrate the actual prevention of sudden cardiac death, this potential benefit from ventricular arrhythmia reduction should not be used in defining indications for antiarrhythmic drug use.

The only established indication for the treatment of ventricular arrhythmias, as of this date, is the reduction or elimination of symptoms demonstrated to be secondary to the ventricular arrhythmia. One should document that symptoms reported by patients are due to a specific ventricular arrhythmia because often there is a poor correlation between what is presumed to be a ventricular arrhythmia-related symptom and, in fact, the presence of such an arrhythmia.[4] When the symptom from the ventricular arrhythmia is hemodynamically important such as syncope, ischemia, cardiac failure or collapse, then the benefit of its removal has a major impact on the patient's life. In this setting, the risks of antiarrhythmic drug therapy reach a different threshold of concern. Obviously, when the only indication for antiarrhythmic drug therapy for the treatment of ventricular arrhythmias is the elimination of nonhemodynamically important symptoms such as palpitations or lightheadedness, which would be only a minor benefit to the patient's life, then the potential risk of drug therapy becomes paramount. For example, if a patient with benign or potentially lethal ventricular arrhythmias[5,6] is being treated only for the purpose of eliminating life-style–limiting palpitations, the benefit would be graded as "minor." If the drug selected for such therapy had the potential risk of a high rate of noncardiac adverse effects and high rate of organ toxicity such as agranulocytosis, then the risks of such therapy seem to clearly outweigh the potential benefit. On the other hand, if a patient had recurrent syncope due to a malignant life-threatening ventricular arrhythmia such as paroxysmal sustained monomorphic ventricular tachy-

TABLE I Risks Versus Benefits of Antiarrhythmic Drug Therapy

	Degree of Importance
Benefits	
Reduction in sudden cardiac death	Major
Reduction in hemodynamic symptoms such as syncope or worse	Major
Reduction in nonhemodynamic symptoms such as palpitations & dizziness	Minor
Risks	
Noncardiac side effects	Minor
Organ toxicity	Major
Cardiac side effects	Minor-Major
Proarrhythmia	
Heart failure	
Conduction defects	

cardia, then the potential benefit of eliminating such hemodynamically important consequences would be graded as "major." Risk with such drug therapy such as noncardiac side effects or the occurrence of non–life-threatening proarrhythmia or heart failure would produce a low threshold of concern. Even a major risk such as the potential for organ toxicity might also be less of a problem if that organ toxic rate was quite low.

Table II details the comparison of the available oral antiarrhythmic drugs for the treatment of ventricular arrhythmias (in the United States) and compares these drugs with moricizine, the focus of this symposium. Before the CAST,[2] encainide and flecainide were regarded as having the best benefit vs risk ratio for therapy in patients with symptomatic ventricular arrhythmias.[7] This decision was based on their potential for suppression of ventricular arrhythmia as the most effective compared with drugs with classes IA, IB, II and III action.[8] In addition, no antiarrhythmic drug had a lower noncardiac adverse-effect rate, potential for organ toxicity, or potential for early proarrhythmia or induction of heart failure in patients with benign or potentially lethal ventricular arrhythmias. Conversely, drugs with class IC action were considered to be toward the end of the algorithm for drug selection in patients with malignant ventricular arrhythmias[8] because encainide and flecainide had no better efficacy than other antiarrhythmic agents, yet they had the highest potential for proarrhythmia. Nevertheless, the benefit of reducing hemodynamically important symptoms in patients with malignant ventricular arrhythmias is a major one; therefore, although the risks of proarrhythmia may be high (about 15 to 20%),[9–11] the benefit vs risk ratio would be such that drugs with class IC action would still be considered for therapy in such patients, but obviously not until other drugs with better profiles had first demonstrated lack of success.

TABLE II Comparative Risks of Antiarrhythmic Agents

			LV Function at Baseline			
			Normal		Abnormal	
	NCAE	Organ Toxicity	Pro-A	CHF	Pro-A	CHF
Class I						
A						
Quinidine	High	Mod	Mod	None	Mod	None
Procainamide	High	High	Mod	Low	Low	Low
Disopyramide	High	None-low	Mod	Mod	Low	High
B						
Tocainide	High	High	Low	None	Low	None
Mexiletine	High	Low	Low	None	Low	None
C						
Encainide	Low	None-low	Low	None	High	Low
Flecainide	Low	None-low	Low	Low	High	High
D						
Moricizine	Low	Low	Low	Low	Low	Low
Class II						
β blockers	Low	None-low	Low	Low	Low	Mod
Class III						
Amiodarone	High	Highest	N/A	N/A	Low	Low

CHF = congestive heart failure; N/A = not applicable; NCAE = noncardiac adverse effects; Pro-A = proarrhythmia.

ALGORITHM FOR ANTIARRHYTHMIC DRUG THERAPY FOR PATIENTS WITH VENTRICULAR ARRHYTHMIAS

When one considers the antiarrhythmic drugs listed in Table II and integrates the risk vs benefit data available for therapy, an algorithm for the selection of antiarrhythmic drug use can be formulated. Such an algorithm must be considered a "personal approach" since no controlled scientific comparative data exist that precisely estimates risk vs benefit ratios among the marked heterogeneous groups of patients under consideration. Table III details this suggested algorithm in relation to the 2 principal indications available for therapy of ventricular arrhythmias, namely, reduction of nonhemodynamic symptoms such as palpitations or dizziness as would be found in patients with benign or potentially lethal ventricular arrhythmias[5,6] or the reduction of hemodynamic symptoms such as syncope or worse that would be found in patients with malignant ventricular arrhythmias. If the physician determines that a reduction of nonhemodynamically important symptoms is worth the cost and the potential risk inherent in any drug, we would prefer initiating therapy with one of the available β blockers because of their low risk of noncardiac adverse effects, organ toxicity, proarrhythmia and congestive heart failure in patients with reasonably preserved left ventricular function at rest. To date, only acebutalol and propranolol are approved by the Food and Drug Administration for control of ventricular arrhythmias. We select these agents as first-line despite

TABLE III Algorithm for Antiarrhythmic Drug Use for Ventricular Arrhythmias

Indication	Drug Selection
Reduction of nonhemodynamic symptoms such as palpitations, dizziness	β blockers → moricizine → encainide or flecainide → mexiletine or disopyramide → quinidine/procainamide/tocainide
Reduction of hemodynamic symptoms such as syncope or worse	Moricizine → quinidine or procainamide → IA + IB → IC → amiodarone

the fact that their relative efficacy is clearly less than drugs with class IC action, moricizine or quinidine.[8] Our selection of β blockers as first-line is also influenced by the fact that these agents have been shown to reduce sudden cardiac death at least in a postmyocardial infarction population although the mechanism of sudden death reduction is unknown.[1] We would then choose moricizine after β blockers because of its relatively high efficacy rate (about two-thirds of patients responding with an adequate reduction in ventricular premature complexes and nonsustained ventricular tachycardia), which is comparable to or better than all other class I agents except those with class IC action. We prefer moricizine over drugs such as encainide or flecainide because it also has a comparable low rate of noncardiac adverse effects, organ toxicity, proarrhythmia and new heart failure, but to date, at least in the CAST study, moricizine has not been shown to increase the potential for sudden cardiac death.[2] We would be reluctant to administer drugs after moricizine for this indication because of the relatively minor benefit that treatment for this indication affords. However, there are patients whose symptoms disturb their lifestyle sufficiently that when β blockers or moricizine fail to alleviate symptoms, other antiarrhythmic drugs, even though they have higher risks, should be considered. In patients without left ventricular dysfunction or previous myocardial infarction, we would still administer encainide or flecainide before drugs with IA or IB action. This position is taken because the potential rate of proarrhythmia with drugs such as quinidine appears to be higher than that with encainide or flecainide in patients with normal left ventricular function and that in postmyocardial infarction trials, drugs such as mexiletine (IB) have demonstrated increased mortality compared with placebo.[12,13] We would not choose to use encainide or flecainide in the treatment of patients with normal cardiac structure and symptomatic ventricular arrhythmias unless the benefit to the patient was believed to be greater than their theoretical increased risk of sudden cardiac death. Beyond drugs with class IC action, we would select drugs such as mexiletine or disopyramide, which have relatively low risk of organ toxicity compared with drugs such as quinidine, procainamide and tocainide.

In patients with malignant ventricular arrhythmias, the principlal indication for therapy would be the reduction of hemodynamically important symptoms. We would now choose moricizine as first-line therapy in light of its demonstrated low risk of proarrhythmia and congestive heart failure in this patient subgroup.[14] It also has a low rate of noncardiac adverse effects and organ toxicity compared with other antiarrhythmic drugs that have previously been considered first-line such as quinidine and procainamide (Table II). If therapy with moricizine is unsuccessful, we would then administer drugs with class IA action because they have less cardiac adverse effect rates such as proarrhythmia than drugs with class IC action which we use at the end of this spectrum. The potential of combining drugs with IA or IB action would place them before drugs with IC action and, finally, we would select the most toxic antiarrhythmic drug, amiodarone, as the last drug of choice in this sequence.

The use of any algorithm must be tailored to the basic underlying cardiovascular condition of the patient who is undergoing indicated drug therapy. The choice of drugs will depend on the presence of underlying sinus node and conduction disease, use of certain concomitant medications, presence of co-existing medical conditions that may interact with the adverse-effect potential of the drug, coexistence of supraventricular arrhythmias and other factors.

REFERENCES

1. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis 1985;27:335–371.*

2. Harrison DC. Antiarrhythmic drug classification: new science and practical application. *Am J Cardiol 1985;56:185–187.*

3. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Increased mortality due to encainide or flecainide in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med 1989;321:406–412.*

4. Zeldis SM, Levin BJ, Michelson EL, Morganroth J. Cardiovascular Complaints: correlation with Cardiac Arrhythmias on 24-hour ECG Monitoring. *Chest 1980;78:456–462.*

5. Morganroth J. Premature ventricular complexes: diagnosis and indications for therapy. *JAMA 1984;252:673–676.*

6. Bigger JT. Identification of patients at high risk for sudden cardiac death. *Am J Cardiol 1984;54:3D–8D.*

7. Morganroth J, Horowitz LN. Antiarrhythmic drug therapy 1988: for whom, how and where? *Am J Cardiol 1988;62:461–465.*

8. Morganroth J. Ambulatory ECG monitoring in the evaluation of new antiarrhythmic drugs. *Circulation 1986;73:II:II-92–II-97.*

9. The Encainide-Ventricular Tachycardia Study Group: (coordinated by Morganroth J, Horowitz LN). Treatment of Resistant ventricular tachycardia with encainide hydrochloride. *Am J Cardiol 1988;62:571–575.*

10. Morganroth J, Horowitz LN. Flecainide: its proarrhythmic effect and expected changes on the surface electrocardiogram. *Am J Cardiol 1984;53:89B–94B.*

11. Morganroth J, Anderson JL, Gentzkow GD. Classification by type of ventricular arrhythmia predicts frequency of adverse cardiac events from flecainide. *JACC 1986;8:607–615.*

12. Chamberlain DA, Jewett DE, Julian DG, Campbell RWF, Boyle DMCD, Shanks BG. Oral mexiletine in high risk patients after myocardial infarction. *Lancet 1980;2:1324–1327.*

13. IMPACT Research Group. International mexiletine and placebo antiarrhythmic coronary trial: I. Report on arrhythmic and other findings. *JACC 1984;6:1148–1163.*

14. Morganroth J, Pratt C. Prevalence and characteristics of proarrhythmia from moricizine (ethmozine). *Am J Cardiol 1989;63:172–176.*

Discussion

Dr. Joel Morganroth (New York, New York): Dr. Bigger, what would be the response to moricizine in patients with preexisting bundle branch or bifascicular, even trifascicular, block? Also, is there any information about changes in pacemaker threshold in patients on moricizine?

Dr. J. Thomas Bigger (New York, New York): Very little information is available. I think we would expect the same kind of thing you would see with any drug with class IA action. This drug has a fairly substantial effect on the HV interval. In fact, if anything, it has a greater effect than one usually sees with quinidine or procainamide. So, we should be cautious in this group of patients. I think you know that even drugs such as encainide and flecainide, although they do increase pacing thresholds, do not usually present a clinical problem.

Participant: I believe that the Cardiac Arrhythmia Suppression Trial has shown that the ventricular premature complex suppression hypothesis has little support for it. I am not so sure that one should be too dogmatic that it's ruled out because encainide and flecainide may have caused a toxic effect, the reason for the increased mortality seen. While encainide and flecainide may have been showing a slightly beneficial effect from a placebo baseline mortality of 1.5%, toxic effect may have pushed the mortality up rather than necessarily in validating totally the ventricular premature complex hypothesis. Studies with quinidine, disopyramide and mexilitine do not suggest that the hypothesis will be easily resurrected with other class I drugs.

Dr. Morganroth: Physicians like to use blood level monitoring as a means to decide whether the drug has reached a toxic effect or whether more drug is required to reach an effect. How does the pharmacology of moricizine help us to decide whether to recommend the use of blood level monitoring in patients treated with this agent?

Dr. Lyle A. Siddoway (Washington, D.C.): While I think from the usual way that we use blood levels predicting efficacy, they are of no use in moricizine therapy. The only reason I might ever think about measuring them would be if you wanted something to compare if the patient down the road loses efficacy and you are concerned about compliance. Actually when you look at therapeutic ranges for all antiarrhythmics you find that the data they are based on are for the most part poor.

Participant: Are there data available on moricizine's use in animal models regarding changes in threshold of ventricular fibrillation? This question comes to mind: Could a late proarrhythmic effect be due to a change in threshold of ventricular fibrillation?

Participant: There are no data that we know about on this issue.

Dr. Morganroth: Is moricizine induction of its own metabolism of practical significance clinically or more of a pharmacological interest?

Dr. Siddoway: Well it doesn't look like it is clinically important. I guess what you might think is that it induces its own metabolism, and the concentration is lower after 1 week of treatment so that you may need to increase the dose. The drug is probably creating active metabolites as it increases its own metabolism. If you look at efficacy parameters or electrocardiographic interval changes, there are no differences as the moricizine plasma level decreases. So this appears not to be a clinically important issue.

Dr. Morganroth: In congestive heart failure the pharmacokinetics of moricizine appeared to undergo little change. What are the data in renal and hepatic failure patients?

Dr. Henry Pieniaszek (Wilmington, Delaware): In cirrhotic patients we only have data on 3 patients, and there appears to be a 2.5-fold increase in oral clearance and in the half-life of the parent compound. I do not know what the relationship will be in the clinic. In renal failure patients we have, so far, not seen any major change.

Dr. Morganroth: What do we know about moricizine's effect in supraventricular arrhythmias?

Dr. Sara Armstrong Mahler (Wilmington, Delaware): We have limited data in the United States. In the Soviet Union there has been a fair amount of data that demonstrate approximately a 70% response rate in patients with preexcitation in stopping reentrant arrhythmias. I believe Du Pont will be making a decision shortly as to whether we will pursue the supraventricular arrhythmia claim.

Dr. Untereker: What do we know about the long-term safety of moricizine administration?

Dr. Mahler: As of February 1, 1987, 1,374 patients had received moricizine. Over 200 of these had been in clinical pharmacology studies and altogether there was a mean duration of dosing of 6 months. Over 520 patients had been dosed for more than 1 month of which 239 have had moricizine for longer than 1 year. Each of these patients was seen every 3 months for the first couple of years and then at least every 6 months thereafter. Therefore, we have a very large data base on long-term efficacy and safety regarding moricizine.

Dr. Craig M. Pratt (Houston, Texas): Could I just comment on that because having seen the data bases of many drugs in patients who have been followed for a year, I know for a fact between Dr. Morganroth and myself, we have placebo-pulsed at 1 year or more at least 100 of those patients in order to show that the arrhythmia comes back, and with reinitiation of therapy the arrhythmia goes away. It is true that in about 20% of those patients the arrhythmia does not come back. I think there is more data long-term on moricizine than any other drug that I know of. While I totally agree we need more information, especially from long-term controlled trials, the fact of the matter is anybody in the audience that thinks that some other drug has all this wonderful long-term information is mistaken.

Dr. Edward Platia (Washington, D.C.): Among the electrocardiographic effects that were shown, is it correct that moricizine does not change the QT interval?

Dr. Pratt: Any change in the QT interval seen on moricizine has been clinically unimportant.

Dr. Platia: Dr. Bigger presented the electrophysiologic effects and noted that moricizine significantly decreased the QT and therefore might be useful in patients with torsades de pointes and long QT situations.

Dr. Bigger: I didn't say that moricizine would be useful to treat torsades de pointes. However, I do think a drug that accelerates repolarization in ventricular tissue and has been shown to suppress artificially created early afterdepolarizations and triggered activity (a tissue model of torsades) by accelerating repolarization would be unlikely to cause torsades. This is a prediction based on electrophysiologic properties of this agent.

Dr. Toby Engel (Philadelphia, Pennsylvania): In patients in whom sustained ventricular tachycardia of the same form was induced with moricizine, what was the change in cycle length? And second, disregarding the complexities of the various stimulation protocols that were used, in patients in whom monomorphic ventricular tachycardia was reduced at baseline, was there a less than expected incidence of polymorphic ventricular tachycardia or ventricular fibrillation induced with the drug?

Dr. Leonard N. Horowitz (Philadelphia, Pennsylvania): The mean slowing in tachycardia is intermediate between that reported with the class IC drugs and that reported with the class IB drugs. With the IA drugs, the amount of slowing shows a tremendous amount of variability from a great deal to none at all. There is a modest average increase in cycle length with a very wide variation. So there is moderate slowing when the arrhythmia remains inducible. There have been no dose-response studies of that phenomenon. Most of the patients in the data base had a single study on moricizine rather than 2 or 3. There really are no data on your second question.

Dr. Bigger: How do you judge moricizine compared to other drugs of class IA action in the malignant arrhythmia group being assessed by electrophysiologic methods?

Dr. Horowitz: There really are no direct comparative data. I think there are 3 major concerns in deciding where you put a drug in an electrophysiologic approach in patients with malignant arrhythmias: efficacy of the drug, overall toxicity (with proarrhythmia certainly one of the major concerns), and the length it takes to achieve a semblance of steady state. So, if you have a drug that takes 2 weeks to reach steady state, even if it is a wonderful drug, it is very difficult to evaluate that drug first. I think that moricizine fits in very nicely and would be used early, particularly because one can achieve steady state reasonably quickly and adjust dosage. It is also tolerated very well early. Its efficacy in the electrophysiology laboratory, like most of the drugs, is in the 20% range. I think that the IA drugs may have slightly better efficacy, but not statistically different, perhaps at about 25%. I think the IC drug may have slightly lower efficacy, again not statistically significant, and I think that the only drugs that that were less often effective in the electrophysiologic model would be the IBs at about 10%. Amiodarone becomes a problem because of its long half-life. I think and hope the argument as to whether the physiologic testing is predictive of amiodarone and its long-term effects is resolved.

If you study someone at 1 or 2 weeks and then study them at 1 or 2 months, you do pick up some additional patients whose arrhythmias become noninducible. Because of difficulty with evaluating efficacy and chronic toxicity, amiodarone should remain last in the cascade of drugs you choose. When looking at the individual patient, moricizine, procainamide and quinidine are probably the best drugs to test early.

Participant: In future studies do you think we ought to extend the dose range upward to increase efficacy?

Dr. Horowitz: Yes. With a lot of drugs, it's a problem to use higher doses before you get more toxicity such as heart failure and proarrhythmia. The patients have more severe cardiac and renal disease so they don't metabolize or excrete the drugs as well. It does appear that these patients can tolerate higher doses of moricizine, however, both from the electrocardiographic effects and from the noncardiac toxicity issue as well.

Participant: Is electrophysiologic testing valuable in predicting long-term clinical efficacy for moricizine?

Dr. Horowitz: The chief flaw with the data relative to the electrophysiologic testing of moricizine is that there were a number of small studies, each with somewhat different criteria that were reanalyzed with a uniform set of criteria. There were a small number of deaths and a few sudden deaths—obviously due to ineffectiveness of the drug. If you look at the percentages over time, they are really not that much different than other data on drugs with IA, IB and IC actions or amiodarone. So the number of patients who had recurrent malignant arrhythmias was not particularly surprising. There are a lot of reasons for a striking fall-off in the number of patients who remain on moricizine long-term. Some have discontinued because of lack of efficacy in regard to the frequency of unsustained ventricular tachycardia on Holter monitoring. Others were discontinued because of long-term adverse effects or such effects were believed to be due to the drug but were not rechallenged.

Some drugs were discontinued because of myocardial infarction, bypass graft surgery and the like, and others because of administrative causes. Therapy in at least half of the patients was discontinued probably because of reasons that we are not particularly concerned about. Finally, my view is that when one looks at the fall-off, it is not terribly different from what would be seen from the limited data for other drugs with class I antiarrhythmic action.

Dr. Sunil Das (Ann Arbor, Michigan): What is the experience in the treatment of arrhythmias in patients who have symptomatic states with structurally normal hearts?

Dr. Pratt: One population that has been studied are patients with mitral valve prolapse who have symptomatic arrhythmias. In 1986, in *The American Journal of Medicine*, we reported our experience with 17 patients with mitral valve prolapse who were extremely bothered by side effects from drugs and continued to be bothered by their arrhythmias despite having normal ventricles.

Over a mean of about 15 months of therapy, we had excellent results from moricizine.

Dr. Bigger: I want to point out that moricizine's efficacy was apparently relatively similar across a wide range of heart failure and function as measured by ejection fraction as shown by Dr. Podrid. Is that strikingly different than your experience with other agents?

Dr. Philip J. Podrid (Boston, Massachusetts): The experience that I reported on is principally in patients with ventricular tachycardia and ventricular fibrillation who usually have poor left ventricular function. The data are not from a wide range in type of patients with ventricular arrhythmias. I don't believe that such data bases have been analyzed in this fashion, but, in general, the experience I have had with a whole list of drugs in a large group of patients suggests that there is an association between efficacy and left ventricular function. We also have seen that same thing for moricizine.

Dr. Bigger: In the Cardiac Arrhythmia Pilot Study, the percentage reaching efficacy using Holter monitoring criteria was substantially lower for encainide and flecainide in patients with ejection fraction less than 0.30. The gradient seemed to be much less steep or maybe even nonexistent for moricizine.

Dr. Podrid: That is my feeling also. In the Cardiac Arrhythmia Pilot Study, there certainly was a difference between encainide and flecainide as compared to moricizine. Certainly, for drugs such as propafenone, tocainide and encainide there has been a relationship between efficacy and left ventricular function.

Participant: There appears to be an enormous dissociation between symptoms reported by the patient and what is observed on Holter monitoring. I wonder if it isn't time for a placebo-controlled trial in this group of patients?

Dr. Morganroth: This is an extremely important point that you make. In fact, The Food and Drug Adminstration has challenged the pharmaceutical industry as well as investigators to show that antiarrhythmic drugs can reduce symptoms. No one has been successful at documenting that relationship to date. As we know, there is a poor correlation between patient complaints of palpitation and the concomitant observation on Holter monitoring of a ventricular arrhythmia that may cause these symptoms. Another problem is that the drugs that we use cause dizziness, which of course is a principal symptom we are trying to treat. Thus, it is a very difficult scientific endeavor to do placebo-controlled trials in this area. One could raise the issue of surrogate end point—that if the ventricular arrhythmia was causing the symptoms and you got rid of the arrhythmia, by definition the symptoms would disappear. However, because of the complexity of this issue I am not so certain that this logic would be accepted by most people.

Dr. Das: What is the mechanism of sudden death in patients who have heart failure? Second, as a plea, would you please tell us what you suggest we do with patients who have low ejection fractions and nonsustained ventricular tachycardia? Are we supposed to hold their hands or try to reduce their risk?

Dr. Podrid: Let me answer the second question first. I think there are substantial data to suggest that patients with congestive heart failure and runs of nonsustained ventricular tachycardia have an increased risk. We do not know whether or not that increased risk can be altered by drug therapy. Therefore I do not know what to do with these patients other than I know that they have an increased risk but I don't know if I can alter it. I tell you that my general approach is to be a doctor. If I can find a drug that is effective and safe without making their failure worse and is suppressing their arrhythmia, then I have had a bias to try to suppress those forms of arrhythmias because I do believe that the patient has an increased risk. I do admit right at the outset that I do this without any data.

Regarding the question about mechanism, as you know Holter monitoring studies have shown that patients who have died while wearing this device have infrequently had bradyarrhythmias as the cause of their death and the final common pathway is usually a ventricular tachyarrhythmia. That is not to say it doesn't occur. It is probably far less common. I don't know what happens to patients with significant congestive heart failure. When they die, they usually die of an arrhythmia such as a brady- or tachyarrhythmia as the immediate cause of death. However, the arrhythmias might be precipitated by worsening failure. Ultimately, everyone dies of an arrhythmia for the most part, but what precipitates it may be the congestive heart failure as opposed to the primary event being arrhythmia in these patients. I am certain many of the patients in this regard die of bradyarrhythmia, and usually we don't know the mechanism as we didn't know the mechanism in patients who died in the Cardiac Arrhythmia Suppression Trial. Thus, their deaths could have been from a brady- or a tachyarrhythmia since they were not monitored.

Dr. Engel: I wonder or speculate about something that might be a proarrhythmic element for moricizine. I am going to suggest that should moricizine become more readily available to clinicians, there would be a tendency to use this drug in combination with quinidine and procainamide. The indication for doing this might be obscure but the rationale may be that the patient has responded to quinidine and procainamide, and moricizine provides a drug with a low profile of side effects that doesn't prolong the QT interval and therefore adding it to quinidine or procainamide might be analogous to the use of mexiletine or tocainide. Could you speculate about the dangers of this happening?

Dr. Morganroth: I think the message to clinicians really should be that they should be cautious with their use of antiarrhythmic drugs. To put 2 antiarrhythmic drugs together at the same time is clearly potentially dangerous. One used to do that when there was a limited number of antiarrhythmic drugs available. With more drugs the tendency of course is not to use 2 drugs at the same time that are part of the same class.

Nevertheless, our advice is that no physician should start with combination antiarrhythmic therapy. If one begins therapy with moricizine and it fails, one should

discontinue that agent and use another. If one needs to go to combination therapy, I believe that moricizine should be considered as having a unique electrophysicological profile but having elements of many of the class I subgroups. Thus, I would be cautious about its prominent use with other class I antiarrhythmics until we have specific data in this regard.

Dr. Podrid: In general, I am an advocate of drug combinations but I am talking about their use in patients with serious arrhythmias. Because these patients have such serious arrhythmias and serious heart disease, frequently single drugs do not work and they often need a combination. I always test drugs singly first, as Dr. Morganroth suggested, and never go to a combination as the first thing I do. I usually use a lower dose of both when I combine. I believe combined therapy has a greater possibility of a negative inotropic effect or arrhythmia aggravation, although I have not seen a case of arrhythmia aggravation when 2 drugs were combined without that side effect to begin with. I think the bottom line is that every patient has to be individualized. There is no preferred combination. Each patient is different.

13.12.9

The American Journal of Cardiology

MARCH 20, 1990

A Symposium: Evolving Issues in the Treatment of Hypercholesterolemia

GUEST EDITORS:

William C. Roberts, MD
Chief, Pathology Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland
and Clinical Professor of Pathology and Medicine (Cardiology)
Georgetown University
Washington, D.C.

Gerd Assmann, MD
Director, Institute of Clinical Chemistry
Director, Institute of Arteriosclerosis Research
University of Münster
Federal Republic of Germany

CALCUTTA CENTRAL UNIVERSITY

A YORKE MEDICAL JOURNAL/CAHNERS PUBLISHING COMPANY

The American Journal of Cardiology

MARCH 20, 1990 VOL. 65 NO. 12

A Symposium: Evolving Issues in the Treatment of Hypercholesterolemia

GUEST EDITORS:

William C. Roberts, MD
Chief, Pathology Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland
and Clinical Professor of Pathology and Medicine (Cardiology)
Georgetown University
Washington, D.C.

Gerd Assmann, MD
Director, Institute of Clinical Chemistry
Director, Institute of Arteriosclerosis Research
University of Münster
Federal Republic of Germany

This symposium was held June 18, 1989, in Washington, D.C.,
and was made possible by an educational grant from Merck Sharp & Dohme.

EDITOR IN CHIEF
William C. Roberts, MD

MANAGING EDITOR, SPECIAL PROJECTS
Judith Wagner

PUBLISHER, SPECIAL PROJECTS
Kenton T. Finch

PRODUCTION EDITOR
Joan Gunning

PROOF EDITOR
Mary Crowell

THE AMERICAN JOURNAL OF CARDIOLOGY.® (ISSN 0002-9149) March 20, 1990, Vol. 65, No. 12 (USPS: 505–750).

Member, American Business Press, Inc. and Audit Bureau of Circulations. Published 4 times in January, February, March, June, July, September and October, 3 times in April, May, August and November, and 2 times in December, by The Cahners Publishing Company, a Division of Reed Publishing USA, 275 Washington St., Newton, MA 02158-1630. Terrence M. McDermott, President; Jerry D. Neth, Vice President/Publishing Operations; J.J. Walsh, Financial Vice President/Magazine Division; Thomas J. Dellamaria, Vice President/Production and Manufacturing.

SUBSCRIPTIONS: Solicited only from cardiologists and other physicians. Publisher reserves the right to refuse unqualified subscribers. Subscribers agree that no article or any part thereof published in any editions of the American Journal of Cardiology received under this subscription agreement may be copied, recorded or reproduced in any form or by any means, electronic or mechanical, including, among other things, photocopying or the storing of part or all of such articles on any information retrieval system, without the written permission of the Publisher. Address correspondence regarding subscriptions and changes of address to: THE AMERICAN JOURNAL OF CARDIOLOGY, 44 Cook Street, Denver, Colorado 80206-5800 (1-800-637-6073). Please include your zip code and, in case of change of address, copy of old address label. Changes of address must reach the Journal one month preceding month of issue. Single copy price: Regular issues $10.00; Symposium and special issues $12.00. Subscription rate for individuals in field of publication: United States 1 year $66, 2 years $112, 3 years $158; Canada and all other countries 1 year $105, 2 years $178, 3 years $252; Residents and Medical Students: United States 1 year $33; Canada & all other countries 1 year $85. Institutions: United States 1 year $95, 2 years $162, 3 years $228; Canada & all other countries 1 year $125, 2 years $213, 3 years $300. Air Mail available at additional charge of $150 per year. The Journal is not responsible for replacing missing issues unless the Circulation Department is notified of nonreceipt within 3 months of issue date.

Second class postage paid at Denver, CO, and at additional mailing office. Printed in U.S.A. Trademark™ in U.S. Patent Office. © Copyright 1990 by Reed Publishing USA: Saul Goldweitz, Chairman; Ronald G. Segel, President and Chief Executive Officer. All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording or by any information storage retrieval system, without permission of the copyright owner. Prices on bulk reprints of articles available on request.

The Publisher assumes no liability for any material published in the Journal. All statements are the responsibility of the authors.

MANUSCRIPTS: Address all manuscripts to William C. Roberts, MD, Editor in Chief, the American Journal of Cardiology, 7960 Old Georgetown Road, Suite 2C, Bethesda, Maryland 20814.

POSTMASTER: Send address changes to: The American Journal of Cardiology, 44 Cook Street, Denver, Colorado 80206-5800.

Cahners Publishing Company, A Division of Reed Publishing USA □ Specialized Business Magazines for Building & Construction □ Manufacturing □ Foodservice & Lodging □ Electronics & Computers □ Interior Design □ Printing □ Publishing □ Industrial Research & Technology □ Health Care □ Entertainment.

Publisher's Note

The opinions expressed in this presentation are those of the panelists and are not attributable to the sponsor or the publisher, editor, or editorial board of The American Journal of Cardiology. Clinical judgment must guide each physician in weighing the benefits of treatment against the risk of toxicity. References made in the articles may indicate uses of drugs at dosages, for periods of time, and in combinations not included in the current prescribing information.

Editor's suggestion: The symposium issues for a full year should be bound together separately from the regular issues.

CONTENTS

The American Journal of Cardiology

MARCH 20, 1990 VOL. 65 NO. 12

A SYMPOSIUM: EVOLVING ISSUES IN THE TREATMENT OF HYPERCHOLESTEROLEMIA

1F
Introduction
William C. Roberts and Gerd Assmann

2F
Diffuse Extent of Coronary Atherosclerosis in Fatal Coronary Artery Disease
William C. Roberts

7F
At What Levels of Total Low- or High-Density Lipoprotein Cholesterol Should Diet/Drug Therapy Be Initiated? United States Guidelines
John C. LaRosa

11F
At What Levels of Total Low- or High-Density Lipoprotein Cholesterol Should Diet/Drug Therapy Be Initiated? European Guidelines
Gerd Assmann

16F
Lipid-Lowering Therapy After an Atherosclerotic Event
William C. Roberts

19F
Hydroxymethylglutaryl Coenzyme A Reductase Inhibitors as Monotherapy in the Treatment of Hypercholesterolemia
J. Findlay Walker and Deborah R. Shapiro

23F
Clinical Experience with Lovastatin
Jonathan A. Tobert, Charles L. Shear, Athanassios N. Chremos, and Geraldine E. Mantell

27F
Clinical Benefits and Cost-Effectiveness of Lowering Serum Cholesterol Levels: The Case of Simvastatin and Cholestyramine in the Netherlands
Leon L. Martens, Frans F.H. Rutten, D. William Erkelens, and Carl A.P.L. Ascoop

33F
Can Atherosclerotic Plaques Regress? Anatomic and Biochemical Evidence from Nonhuman Animal Models
Robert W. Wissler and Dragoslava Vesselinovitch

41F
Can Atherosclerotic Lesions Regress? Angiographic Evidence in Humans
David H. Blankenhorn

The American Journal of Cardiology

Introduction

William C. Roberts, MD, and Gerd Assmann, MD

The subjects of the articles included in this symposium initially were presented at a meeting in Washington, D.C., in September 1989. Roberts from Bethesda, Maryland, described both qualitatively and quantitatively the amounts of narrowing by atherosclerotic plaques in the 4 major epicardial coronary arteries in patients with fatal coronary artery disease. The data indicated that about a third of the entire lengths of the major epicardial coronary arteries were narrowed >75% in cross-sectional area by plaques in all subsets of patients with fatal coronary artery disease. Patients with unstable angina pectoris had significantly more coronary narrowing than did patients with other subsets of coronary disease.

La Rosa from Washington, D.C., summarized the recommendations of the Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults in the USA.

Assmann from Münster, West Germany, summarized the guidelines developed by 2 European Consensus Conferences for treating patients with hyperlipidemia.

Roberts from Bethesda, Maryland, developed an argument advocating the use of lipid-lowering drugs in addition to low-fat, low cholesterol diet for virtually all patients with symptomatic atherosclerotic events irrespective of the level of the serum (or plasma) total and low-density lipoprotein cholesterol levels at the time of the symptomatic atherosclerotic event.

Tobert and associates from Rahway, New Jersey, and West Point, Pennsylvania, described preliminary results of an ongoing clinical trial involving 744 patients who received lovastatin for an average of 3.6 years. The drug was very effective and its adverse effects were minimal.

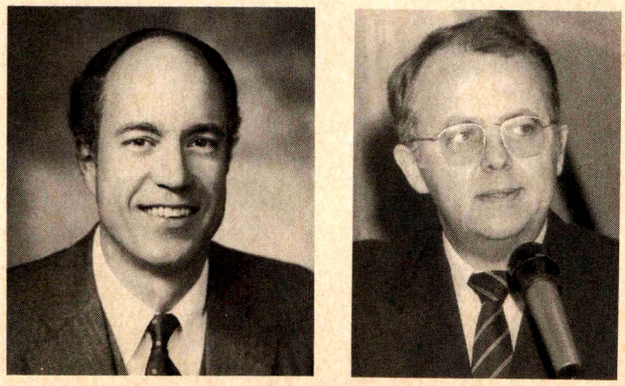
Walker and associates from Rahway, New Jersey, described results of clinical trials in both the USA and in other countries comparing the lipid-lowering effects of lovastatin and simvastatin to those of cholestyramine, gemfibrozil, benzafibrate and probucol in patients with severe hypercholesterolemia. The hydroxymethylglutaryl coenzyme A reductase inhibitors were the most effective in reducing the serum total and low-density lipoprotein levels.

Martens and colleagues from Rotterdam, Maastricht, Utracht and Nieuwegein, The Netherlands, used a model of coronary artery disease incidence from the Framingham study to assess the cost-effectiveness of cholesterol lowering with simvastatin and cholestyramine in the primary prevention of coronary artery disease in the Netherlands. The results suggested that simvastatin therapy was substantially more cost-effective than cholestyramine.

Blankenhorn from Los Angeles, California, summarized results from 3 angiographic trials involving a total of 317 patients. They indicated that angiographic narrowings can be prevented from narrowing further (lack of progression) or can actually become less narrowed (regression) during a 2- to 5-year period when high serum total and low-density lipoprotein levels were lowered by diet or drugs, or both.

Wissler and Vesselinovitch from Chicago, Illinois, summarized anatomic evidence in rabbits and monkeys that atherosclerotic plaques induced by atherogenic diets can regress substantially when the atherogenic diets are eliminated.

Thank you Merck Sharp & Dohme for sponsoring this excellent symposium.



William C. Roberts, MD *(left)* and Gerd Assmann, MD *(right)*

Diffuse Extent of Coronary Atherosclerosis in Fatal Coronary Artery Disease*

William C. Roberts, MD

In 4 subsets of patients with coronary artery disease, the amounts of narrowing of the 4 major epicardial coronary arteries were compared (left main, left anterior descending, left circumflex and right) by atherosclerotic plaques. Among 129 patients studied at necropsy, an average of 2.7 of the 4 arteries were narrowed >75% in cross-sectional area at some point; in control subjects, narrowing was seen in an average of 0.7 arteries. Patients with unstable angina pectoris had a greater incidence of narrowing (3.2 arteries) than did patients with sudden coronary death (2.8), acute myocardial infarction (MI) (2.7) or healed MI (2.3). Each of the 4 major arteries was divided into segments 5 mm in length, and histologic sections were prepared and stained by the Movat method. A total of 6,461 segments were analyzed from the 129 patients and 1,849 from the 40 controls. In the 129 patients, 35% of the 5-mm segments were narrowed 75 to 100% in cross-sectional area (compared with 3% in control subjects). The group with unstable angina had the highest percentage (48%) of severely narrowed segments compared with the groups with sudden coronary death (36%), acute (34%) and healed MI (31%). Only 8% of the 6,461 segments were narrowed ≤25% in cross-sectional area, and virtually none of the 6,461 segments was normal; thus, 92% of the coronary segments were narrowed >25% in cross-sectional area by atherosclerotic plaque alone. Among patients with fatal coronary artery disease studied at necropsy, therefore, the atherosclerotic process is severe and diffuse in the major epicardial coronary arteries.

(Am J Cardiol 1990;65:2F–6F)

Atherosclerotic coronary artery disease (CAD) is the most common cause of death in the Western world. In the United States, 1 person dies every minute because of atherosclerotic CAD, and approximately 6 million persons have symptomatic myocardial ischemia due to this disease. Furthermore, approximately 250,000 coronary artery bypass grafting procedures and a similar number of coronary angioplasties were performed in the United States in 1988.

The evidence is now overwhelming that atherosclerosis is caused by elevated cholesterol levels; the higher the level of total blood cholesterol (specifically low-density lipoprotein cholesterol), the greater the risk of developing symptomatic CAD, the greater the chance of having fatal CAD, and the greater the extent of the atherosclerotic plaques. Conversely, lowering total blood cholesterol decreases the risk of symptomatic or fatal CAD and increases the likelihood that some atherosclerotic plaques will actually become smaller (i.e., regress). Although the coronary arteries have been examined by visual inspection at necropsy for more than 100 years, only recently has the extent of the atherosclerotic process in patients with symptomatic or fatal CAD become appreciated. This article reviews the status of the major epicardial coronary arteries in various subsets of patients with fatal atherosclerotic CAD. A similar review has appeared previously.[1]

NUMBER OF SEVERELY NARROWED MAJOR EPICARDIAL CORONARY ARTERIES

The most common method of describing the severity of CAD in patients with clinical evidence of myocardial ischemia is by the number of major epicardial coronary arteries narrowed >50% in luminal diameter, as determined on angiography. Thus, patients are categorized as having either 1-, 2-, or 3-vessel or "left main" CAD. Because a 50% diameter reduction is generally equivalent to a 75% cross-sectional area narrowing, the latter figure is used as the cut-off point for "significant" as opposed to "insignificant" luminal narrowing at necropsy. Physiologically, arterial flow is not obstructed until the lumen is narrowed >75% in cross-sectional area.

Table I summarizes the number of major (right, left main, left anterior descending and left circumflex) epicardial coronary arteries narrowed >75% in cross-sectional area by atherosclerotic plaque alone in a study of patients with fatal CAD.[1] Among 129 patients with fatal CAD studied at necropsy, 516 major epicardial coronary arteries were examined; of these, 345 arteries (67%) were narrowed 76 to 100% in cross-sectional area at some point by atherosclerotic plaque. Among 40 control subjects

From the Pathology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

Address for reprints: William C. Roberts, MD, Pathology Branch, National Heart, Lung, and Blood Institute, Building 10, Room 2N258, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20892.

*This article in nearly similar form appeared in the August 1, 1989, issue of *The American Journal of Cardiology*.

TABLE I Number of Major (Right, Left Main, Left Anterior Descending and Left Circumflex) Coronary Arteries Narrowed >75% in Cross-Sectional Area by Atherosclerotic Plaque in Fatal Coronary Artery Disease

Coronary Event	Pts (n)	Mean Age (yrs)	No. of Four Arteries/Pt > 75% ↓ in CSA by Plaque				
			4	3	2	1	Mean
Sudden coronary death	31	47	3	20	6	2	2.8
Acute myocardial infarction	27	59	3	14	10	0	2.7
Healed myocardial infarction							
Asymptomatic	18	66	0	7	7	4	2.2
Chronic CHF without aneurysm	9	63	0	3	5	1	2.2
Left ventricular aneurysm	22	61	1	12	6	3	2.5
Angina pectoris/unstable	22	48	10	8	3	1	3.2
Total (%)	129	56	17 (13)	64 (50)	37 (29)	11 (8)	2.7
Controls (%)	40	52	0 (0)	5 (5)	12 (13)	21 (23)	0.7

CHF = congestive heart failure; CSA = cross-sectional area.
Reproduced with permission from *Am J Cardiol.*[1]

(mainly victims of acute leukemia who had no clinical evidence of myocardial ischemia during life), 160 major epicardial coronary arteries were examined; in contrast to the findings in the CAD patients, only 60 arteries (37%) were narrowed >75% in cross-sectional area at some point by plaque. Only 11 (8%) of CAD patients, vs 23% of controls, had a single coronary artery severely narrowed. Severe narrowing was present in 2 arteries in 37 patients (29%) vs 13% of controls, in 3 arteries in 64 patients (50%) vs 5% of controls, and in all 4 major arteries in 17 patients (13%) vs no controls. Overall, then, an average of 2.7 arteries in CAD patients, as opposed to 0.7 in controls, were narrowed >75% in cross-sectional area by plaque.

The numbers of severely narrowed arteries among the various subsets of patients with CAD were similar, with the exception of the group with unstable angina (Table I). Among 31 patients with sudden coronary death,[2] all of whom died outside the hospital (usually within a few minutes of onset of symptoms of myocardial ischemia), an average of 2.8 of the 4 major arteries were severely narrowed; this number was identical to that in 27 patients with transmural acute myocardial infarction (MI),[3] all of whom died in a coronary care unit. Only 2 of the 31 sudden death victims, and none of the 27 acute MI victims, had 1-vessel disease.

Patients with healed MI were separated into 3 subgroups. One subgroup consisted of those who had had an acute MI that had healed, with no subsequent clinical evidence of myocardial ischemia; these patients died from noncardiac causes (usually cancer).[4] Nevertheless, an average of 2.2 of the 4 major coronary arteries were severely narrowed at necropsy in these patients. A second subgroup consisted of patients who had chronic congestive heart failure after healing of an acute MI, but in the absence of a left ventricular aneurysm[5]; this group might be referred to as having "ischemic cardiomyopathy." An average of 2.2 major coronary arteries were severely narrowed in these patients. The other subgroup of patients with healed MI had true left ventricular aneurysms.[6] The average number of severely narrowed major coronary arteries in this group was 2.5.

The third subgroup consisted of 22 patients with unstable angina pectoris, all of whom had undergone coronary artery bypass grafting within 7 days of dying.[7] Preoperatively, all had normal left ventricular function and none had had a clinically apparent acute MI or congestive heart failure at any time. The average number of major coronary arteries severely narrowed by plaque was 3.2, and 10 of the 22 patients had severe narrowing of the left main coronary artery as well as the other 3 major coronary arteries (4-vessel disease). (Bulkley and I[8] found that severe narrowing of the left main coronary artery is usually an indicator that the other 3 major arteries also are severely narrowed.) The unstable angina group thus had the largest average number of severely narrowed major coronary arteries of any of the subgroups, but nevertheless had excellent left ventricular function.

AMOUNTS OF NARROWING IN SEGMENTS OF THE MAJOR CORONARY ARTERIES

Although the classifications of 1-, 2-, 3- and 4-vessel disease have been useful clinically, this type of analysis of severity might be thought of as a qualitative approach. Differences in degrees of coronary narrowing in various subsets of patients with CAD cannot usually be discerned by this approach. To obtain a better appreciation of the extent of the atherosclerotic process in patients with fatal CAD, my colleagues and I began examining 5-mm-long segments of each of the 4 major coronary arteries several years ago. In adults, the average length of the right coronary artery is 10 cm; the left main, 1 cm; the left anterior descending, 10 cm; and the left circumflex, 6 cm. Thus, 27 cm of major epicardial coronary artery are available for examination in each adult. Because each 1 cm is divided into 2 segments, each measuring 5 mm in length, an average of 54 such segments are available for examination in each heart. This approach allows one to ask not only how many of the 5-mm segments are narrowed 76 to 100% in cross-sectional area, but also how many are narrowed 51 to 75%, 26 to 50%, or 0 to 25%. This might be considered a quantitative approach.

The same patients previously described by the qualitative approach also were examined at necropsy by the quantitative approach; the findings are summarized in

TABLE II Amounts of Cross-Sectional Area Narrowing of Each 5-mm Segment of the Four Major (Right, Left Main, Left Anterior Descending and Left Circumflex) Epicardial Coronary Arteries by Atherosclerotic Plaques in Subjects with Fatal Coronary Artery Disease

Subgroup	Pts (n)	Mean Age (yrs)	No. 5-mm Segments	Percent Segments Narrowed 0–25%	26–50%	51–75%	76–100%	Mean Score	Mean % Narrowing/ 5-mm Segments
Sudden coronary death	31	47	1,564	7	23	34	36	2.98	67
Acute myocardial infarction	27	59	1,403	5	23	38	34	3.01	68
Healed myocardial infarction									
Asymptomatic	18	66	924	11	23	35	31	2.87	64
Chronic CHF without aneurysm	9	63	529	11	23	37	29	2.78	61
							31%		
LV aneurysm	22	61	992	4	21	42	33	3.03	68
Angina pectoris	22	48	1,049	11	12	29	48	3.12	70
Total	129	56	6,461	8	21	36	35	2.98	67
Controls	40	52	1,849	31	44	22	3	1.97	32

CHF = congestive heart failure; LV = left ventricular.
Reproduced with permission from *Am J Cardiol.*[1]

Table II. A total of 6,461 segments (each 5 mm in length) were sectioned and later examined histologically. The sections were stained by the Movat method to delineate the internal elastic membrane. The findings in the 129 patients with CAD were compared with those in 40 control subjects, from whom 1,849 segments were obtained. In each coronary subgroup, the 5-mm segments from each of the 4 major coronary arteries were pooled together. With this approach, the amount of narrowing in an individual patient was not discernible. Among the CAD patients, 35% of segments were narrowed 76 to 100% in cross-sectional area by atherosclerotic plaque; in contrast, only 3% were narrowed in controls. The segments narrowed 51 to 75% totaled 36 and 22%, respectively. Thus, 71% of the segments in the CAD patients, and 25% in controls, were narrowed >50% in cross-sectional area by atherosclerotic plaque. In contrast, only 29% of the segments in the CAD patients were narrowed <50% and only 8% even approached normal (i.e., narrowed ≤25% in cross-sectional area). In contrast, 75% of the segments in the control subjects were narrowed <50% and 31% of them were normal or nearly normal. Thus, in the CAD patients, 92% of the 6,461 segments of the 4 major epicardial coronary arteries were narrowed >25% in cross-sectional area by atherosclerotic plaque. Accordingly, the coronary atherosclerotic process is diffuse, rather than focal, in patients with fatal CAD.

Among the various subsets of CAD patients, those with sudden coronary death[2] and acute MI[3] had similar percentages of 5-mm segments narrowed 76 to 100% in cross-sectional area by plaque (36 and 34%, respectively); patients with healed MI[4–6] as a group had the least severe narrowing (31% of segments narrowed >75%), and those with unstable angina pectoris[7] had the most severe narrowing (48% of segments narrowed >75% by plaque).

In an effort to arrive at a single number for the amount of coronary arterial narrowing in each patient, a score system was utilized for each 5-mm segment. Narrowing of 0 to 25% was assigned a score of 1; 26 to 50%, 2; 51 to 75%, 3; and 76 to 100%, 4. The mean score for all 129 patients (or for the 6,461 coronary segments) was 3.0, and that for the 40 control subjects (or 1,849 segments) was 2.0. Using this scoring system, patients with unstable angina again had the most extensive coronary narrowing.

A possible criticism of the analysis of 5-mm segments to quantify coronary arterial narrowing is that the epicardial coronary arteries were fixed in an unphysiologic pressure state—namely, a zero-pressure state—rather than at a systemic arterial diastolic pressure. The degrees of narrowing were conservatively judged to take into account the unphysiologic fixed state. For example, if a segment was between 2 quadrants (51 to 75% and 76 to 100%), the lesser degree of narrowing was always chosen. Second, for any segment in which a portion of wall was collapsed by the fixation process, the degree of narrowing was determined as if the segment was expanded. Most important, the segments narrowed the most (>75% in cross-sectional area) were affected the least by the fixation process. Whether the histologic technique in this study is perfect or flawed, the same technique was in all subsets of coronary patients and all controls. The comparison data are, therefore, highly reliable. Also, regardless of whether the degrees of luminal narrowing are slightly greater or less than those determined by this technique, it is clear that the atherosclerotic process is a diffuse one in nearly all patients with fatal CAD. The accuracy of the technique of determining degrees of cross-sectional area narrowing by estimating from stained histologic sections magnified approximately 40 times is similar (≤5%) to that determined by planimetry.[9]

Another possible concern of the aforementioned quantitative data is its applicability to living patients with symptomatic or other clinical evidence (e.g., positive exercise test results) of myocardial ischemia. I believe that the major difference in coronary arterial narrowing oc-

curs at the stage of conversion from the asymptomatic to the symptomatic myocardial ischemia state, and that there is relatively little difference in degrees of coronary narrowing between the symptomatic and the fatal states. Assessment of the presence of severe, extensive coronary narrowing on angiography during life, as well as by study of the coronary tree at necropsy in patients who had coronary events and later died from noncardiac causes, supports this view. Although only minimal data are available from the latter group, the degrees of coronary narrowing at necropsy are similar to those in other patients with symptomatic myocardial ischemia that proves fatal.[4] Also, of the subsets of CAD patients described, those with unstable angina pectoris had significantly greater degrees of coronary narrowing. Furthermore, these patients were the only subjects in whom the natural course was interrupted by an iatrogenic event, i.e., coronary artery bypass grafting within 7 days of death.

DISTRIBUTION OF SEVERE NARROWING IN THE THREE LONGEST EPICARDIAL CORONARY ARTERIES

In all the quantitative studies described herein, the amount of cross-sectional area luminal narrowing by atherosclerotic plaque in the right, left anterior descending and left circumflex coronary arteries was similar if the 5-mm segments in each of the 3 longest arteries were pooled together from a number of patients. Examination of a single subset of patients with fatal CAD may help to better understand this concept. Among the 27 patients with fatal transmural acute MI, a total of 1,358 segments were analyzed from the right, left anterior descending and left circumflex coronary arteries. The percentages of segments narrowed 0 to 25%, 26 to 50%, 51 to 75% and 76 to 100% were similar in each of these 4 categories in each of the 3 major epicardial coronary arteries. Analysis of the patients with sudden coronary death, healed MI and unstable angina pectoris yielded the same results.

In an individual patient, however, the percentage of 5-mm segments severely narrowed (>75% in cross-sectional area) by atherosclerotic plaque in 1 major epicardial coronary artery may be greater or less than that in another major coronary artery. Nonetheless, if the segments from 1 coronary artery (e.g., right) were pooled together from several patients with fatal CAD and compared with segments from another coronary artery (e.g., left anterior descending) pooled from several patients with fatal CAD, the percentages of segments narrowed in each of the 4 categories of cross-sectional area narrowing in each artery would be similar. The definition of "several" has not yet been established, but, with infrequent exceptions, this principle may apply to as few as 3 patients with pooled 5-mm segments from each of the 3 major coronary arteries. Thus, the quantity of atherosclerotic plaque is similar for similar lengths of the right, left anterior descending and left circumflex coronary arteries. Furthermore, because the amount of atherosclerotic plaque is similar, the amount of resulting luminal narrowing also is similar. The cholesterol thesis might not be tenable if the amount of atherosclerotic plaque were highly different in the different major epicardial coronary arteries, because the same serum cholesterol level presumably is present in each major coronary artery.

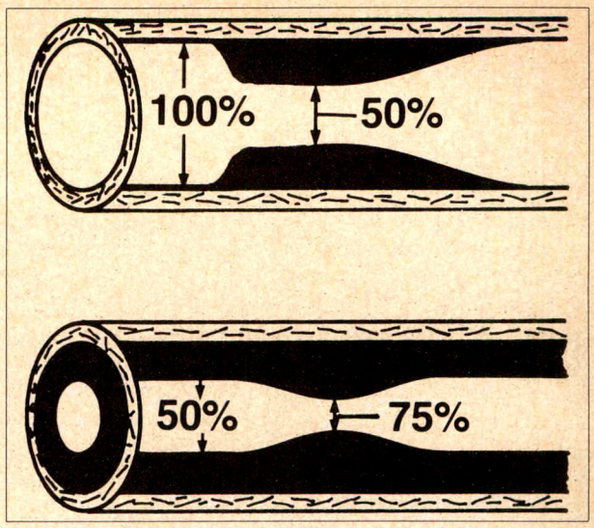


FIGURE 1. Representation of an angiographic view of 2 coronary arteries with luminal plaque. Because the angiogram is a luminogram, and the width of the original arterial lumen is unknown, the least narrowed segment is often presumed to be normal. Comparison of a narrowed segment to a near-normal segment (*upper panel*) provides an accurate measurement of the degree of narrowing, but normal or near-normal segments are infrequent in patients with symptomatic myocardial ischemia. More frequently, severely narrowed segments are simply compared with less severely narrowed segments, but none of the segments approach normal (*lower panel*). (Reproduced with permission from *Am Heart J.*[13])

CLINICAL USEFULNESS OF THE QUANTITATIVE APPROACH

The quantitative information derived at necropsy on the severity and extent of atherosclerosis in the 4 major epicardial coronary arteries in fatal CAD has possible clinical applications in (1) interpreting degrees of coronary narrowing by angiography during life and (2) deciding which of the major coronary arteries requires a conduit at the time of coronary artery bypass grafting.

Without coronary angiography, neither coronary bypass nor angioplasty would be performed. The only way to obtain information on the status of the epicardial coronary arteries during life is with angiography; consequently, this procedure revolutionized the diagnosis of CAD, just as aortocoronary bypass grafting revolutionized the therapy of CAD. However, despite the advantages of angiography, this technique has certain failings. For one, the angiogram is a luminogram, which compares a narrowed segment with a less narrowed segment that is assumed to be normal. The angiogram does not delineate the internal elastic membrane of the artery, and, therefore, the artery's true lumen remains uncertain.

The quantitative studies of fatal CAD mentioned herein demonstrated that 93% of the 5-mm long segments

of the 4 major epicardial coronary arteries were narrowed >25% in cross-sectional area by atherosclerotic plaque. Thus, only 7% of the 5-mm segments even approached normal, and virtually none were normal. In fatal CAD, and probably also in live patients with symptomatic myocardial ischemia, therefore, only rarely can a coronary artery segment that is severely narrowed on angiography be compared with a segment of coronary artery that is normal. In other words, in patients with symptomatic myocardial ischemia, the coronary angiogram measures degrees of narrowing by comparing severely narrowed segments with segments that are simply less narrowed and by no means normal (Fig. 1). Thus, coronary angiograms in patients with symptomatic myocardial ischemia usually underestimate the degrees of luminal narrowing.[10,11]

The unit of measurement for degrees of narrowing on angiography is different from the unit of measurement at necropsy. In the aforementioned anatomic quantitative studies, the unit was cross-sectional area narrowing, whereas the unit used in angiography is diameter narrowing. In general, a 75% cross-sectional area narrowing is equivalent to a 50% diameter reduction, and, therefore, a 50% or more diameter reduction during life has generally been considered the cut-off point between clinically significant and clinically insignificant coronary narrowing.

The second potential clinical application of the information gleaned from the quantitative CAD studies at necropsy is the recognition that the atherosclerotic process in patients with symptomatic myocardial ischemia is usually diffuse and severe, and, therefore, more rather than fewer aortocoronary conduits provide a higher frequency of relief or improvement in symptoms of myocardial ischemia, improvement in results of exercise testing, and prolonged life. Among patients surviving <30 days or at later periods after aortocoronary bypass operations, the amount of severe narrowing in the nonbypassed native coronary arteries is usually similar to that in the bypassed native coronary arteries.[12] Waller and I[12] found from study at necropsy of 102 patients dying either early (≤60 days) or late (2.5 to 108 months, mean 35) after bypass operations that the bypassed and nonbypassed native coronary arteries had similar degrees of severe luminal narrowing by atherosclerotic plaques. In 213 of 226 bypassed native arteries (94%) and in 73 of 80 nonbypassed native arteries (91%), the lumens were narrowed >75% in cross-sectional area by atherosclerotic plaque. Bypass of the native arteries was not avoided because they were too small or severely narrowed distally, but, rather, because the lumens were judged to be insufficiently narrowed (on angiography) to warrant insertion of a conduit. Thus, if 2 of the major coronary arteries are found to be severely narrowed on angiography and the third major artery is "insignificantly" narrowed, and if bypass is to be performed, an argument could be made for insertion of a conduit in all 3 major coronary arteries. Of course, insertion of a conduit in an insignificantly narrowed artery is potentially dangerous. Nevertheless, it may be more prudent to have too many conduits rather than too few. Three-vessel disease is far more frequent than is 2-vessel disease at necropsy, and even when only 2 of the 3 major arteries are narrowed >75% in cross-sectional area, the third is usually narrowed 51 to 75%. Thus, an appreciation of the diffuse nature of coronary atherosclerosis in fatal CAD, and probably also in symptomatic myocardial ischemia, encourages the use of more, rather than fewer, conduits in coronary bypass operations.

REFERENCES

1. Roberts WC. Qualitative and quantitative comparison of amounts of narrowing by atherosclerotic plaques in the major epicardial coronary arteries at necropsy in sudden coronary death, transmural acute myocardial infarction, transmural healed myocardial infarction and unstable angina pectoris. *Am J Cardiol 1989;64:324–328.*

2. Robert WC, Jones AA. Quantitation of coronary arterial narrowing at necropsy in sudden coronary death. Analysis of 31 patients and comparison with 25 control subjects. *Am J Cardiol 1979;44:39.*

3. Roberts WC, Jones AA. Quantification of coronary arterial narrowing at necropsy in acute transmural myocardial infarction: analysis and comparison of findings in 27 patients and 22 controls. *Circulation 1980;61:786–790.*

4. Virmani R, Roberts WC. Non-fatal healed transmural myocardial infarction and fatal non-cardiac disease. Qualification and quantification of coronary arterial narrowing and of left ventricular scarring in 18 necropsy patients. *Br Heart J 1981;45:434–441.*

5. Virmani R, Roberts WC. Quantification of coronary arterial narrowing and of left ventricular myocardial scarring in healed myocardial infarction with chronic eventually fatal, congestive cardiac failure. *Am J Med 1980;68:831–838.*

6. Cabin HS, Roberts WC. True left ventricular aneurysm and healed myocardial infarction. Clinical and necropsy observations including quantification of degrees of coronary arterial narrowing. *Am J Cardiol 1980;46:754–763.*

7. Roberts WC, Virmani R. Quantification of coronary arterial narrowing in clinically-isolated unstable angina pectoris. An analysis of 22 necropsy patients. *Am J Med 1979;67:792–799.*

8. Bulkley BH, Roberts WC. Atherosclerotic narrowing of the left main coronary artery. A necropsy analysis of 152 patients with fatal coronary heart disease and varying degrees of left main narrowing. *Circulation 1976;53:823–828.*

9. Isner JM, Wu M, Virmani R, Jones AA, Roberts WC. Comparison of coronary arterial luminal narrowing determined by visual inspection of histologic sections under magnification among three independent observers and comparison to that obtained by video planimetry. An analysis of 559 five-millimeter segments of 61 coronary arteries from eleven patients. *Lab Invest 1980;42:566–570.*

10. Arnett EN, Isner JM, Redwood DR, Kent KM, Baker WP, Ackerstein H, Roberts WC. Coronary artery narrowing in coronary heart disease: comparison of cineangiographic and necropsy findings. *Ann Intern Med 1979;91:350–356.*

11. Isner JM, Kishel J, Kent KM, Ronan JAJ, Ross AM, Roberts WC. Accuracy of angiographic determination of left main coronary arterial narrowing. Angiographic-histologic correlative analysis in 28 patients. *Circulation 1981;63:1056–1064.*

12. Waller BF, Roberts WC. Amount of narrowing by atherosclerotic plaque in 44 nonbypassed and 52 bypassed major epicardial coronary arteries in 32 necropsy patients who died within 1 month of aortocoronary bypass grafting. *Am J Cardiol 1980;46:956–962.*

At What Levels of Total Low- or High-Density Lipoprotein Cholesterol Should Diet/Drug Therapy Be Initiated? United States Guidelines

John C. LaRosa, MD

Guidelines for the detection, evaluation and treatment of hypercholesterolemia in adults have been established in the United States. These guidelines recommend that total cholesterol levels be used for screening purposes. Total cholesterol levels >240 mg/dl are considered "high," those from 200 to 239 mg/dl "borderline," and those <200 mg/dl "normal," regardless of the person's age or gender. All persons in the high category, as well as those in the borderline category who have other risk factors or established vascular disease, require measurements of low-density lipoprotein (LDL) cholesterol levels. LDL cholesterol levels are used to guide the selection of treatment. Patients with LDL cholesterol levels >130 mg/dl are candidates for active diet therapy. Those whose LDL cholesterol levels are 160 to 190 mg/dl after 3 to 6 months of diet therapy are candidates for drug therapy. A high-density lipoprotein (HDL) level <35 mg/dl is considered a risk factor and may influence the level of LDL at which drug therapy is initiated. Some observers have expressed concern that these guidelines overemphasize LDL cholesterol at the expense of total cholesterol, HDL cholesterol and triglyceride levels. Nevertheless, the guidelines have been broadly accepted and currently serve as the basis for a widespread public-health education program.

(Am J Cardiol 1990;65:7F–10F)

From the Department of Medicine and Health Care Sciences, George Washington University Medical Center, Washington, D.C.

Address for reprints: John C. LaRosa, MD, George Washington University Medical Center, Suite 2500 North, 901 23rd Street, NW, Washington, D.C. 20037.

The relation between circulating cholesterol levels and coronary atherogenesis has been recognized for some time, but has also generated considerable controversy. The current focus on this issue stems from the fact that, in the opinion of many observers, the evidence causally linking circulating cholesterol levels and coronary artery disease has now become overwhelming.

Most recently, the wealth of animal, epidemiologic and genetic data has been extended by strong indications that altering circulating cholesterol fractions (in particular, lowering levels of low-density lipoprotein [LDL] cholesterol) can arrest, prevent and even reverse the progression of coronary atherosclerosis.[1–4] To address the important public health issues raised by this evidence, the National Heart, Lung, and Blood Institute organized the National Cholesterol Education Program in 1987. Cosponsors of this effort include most of the major health organizations, representing both providers and consumers interested in heart disease prevention and treatment.[5]

The first of several panels to address major facets of the cholesterol issue was the Expert Panel on the Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (referred to as the Adult Treatment Panel). This group was empaneled in the autumn of 1987 and made its final report the following year. The report may be read in its entirety elsewhere.[5] This presentation briefly reviews the Adult Treatment Panel recommendations, discusses some of the controversies generated by the guidelines, and speculates on the implications for medical practice.

RECOMMENDATIONS FOR SCREENING

The Adult Treatment Panel report recommended that all persons older than age 20 years know their total cholesterol levels. The report fell short of a blanket endorsement of widespread public screening, because the committee believed that neither the necessary technology nor experience in the public health and medical communities was, as yet, in place. Rather, the report emphasized measurement of total circulating cholesterol, without regard to fasting status, in the course of any appropriate medical encounter.

According to the approach suggested in the report, persons with total cholesterol levels <200 mg/dl are to be termed "normal" and require nothing more than encouragement to follow the same relatively low cholesterol, low saturated fat diet recommended for all Americans (Table I).[5] In addition, they should be advised to have their total

TABLE I Initial Classification and Recommended Follow-Up Based on Total Cholesterol

Classification	
<200 mg/dl	Desirable blood cholesterol
200–239 mg/dl	Borderline-high blood cholesterol
≥240 mg/dl	High blood cholesterol
Recommended follow-up	
Total cholesterol <200 mg/dl	Repeat within 5 years
Total cholesterol 200–239 mg/dl	
Without definite CAD or 2 other CAD risk factors (1 of which can be male sex)	Dietary information and recheck annually
With definite CAD or 2 other CAD risk factors (1 of which can be male sex)	Lipoprotein analysis; further action based on LDL-cholesterol level
Total cholesterol ≥240 mg/dl	

CAD = coronary artery disease.
Adapted with permission from *Arch Intern Med.*[5]

TABLE III Classification of Low-Density Lipoprotein Cholesterol Levels

<130 mg/dl	Desirable low-density lipoprotein cholesterol
130–159 mg/dl	Borderline-high-risk low-density lipoprotein cholesterol
≥160 mg/dl	High-risk low-density lipoprotein cholesterol

Adapted with permission from *Arch Intern Med.*[5]

TABLE IV Secondary Causes of High-Risk Low-Density Lipoprotein Cholesterol

- Hypothyroidism
- Nephrotic syndrome
- Diabetes mellitus
- Obstructive liver disease
- Drugs, particularly progestins and anabolic steroids

Adapted with permission from *Arch Intern Med.*[5]

cholesterol measured again in 5 years. This latter recommendation assumes, of course, that no medical indication for an early repeat measurement has intervened.

Persons with total cholesterol levels >240 mg/dl, however, are unequivocally considered to have high blood cholesterol. Currently, 25% of adult Americans qualify for this category. Persons who have high total cholesterol must, at least temporarily, be regarded as patients requiring further evaluation. Such evaluation consists of first measuring fasting triglyceride and high-density lipoprotein (HDL) cholesterol levels, as well as repeating the measurement of total cholesterol. These values, in turn, can be used to estimate LDL cholesterol, according to the following formula[6]: LDL cholesterol = total cholesterol − (HDL cholesterol + triglycerides/5). As long as the fasting triglyceride levels are <400 mg/dl, this formula is valid and, in fact, may be so even up to triglyceride levels of 800 mg/dl.

Persons in the "borderline-high" category (total cholesterol levels of 200 to 239 mg/dl) should, at a minimum, be instructed to follow a diet low in cholesterol and saturated fat and be rechecked annually. The panel recommended that only those with established atherosclerotic vascular disease or 2 or more other coronary risk factors (one of which is male gender [Table II]) require further lipoprotein analyses. Nonetheless, the report left ample room for physician discretion in determining the extent of the work-up on a patient in the borderline category.

TABLE II Coronary Artery Disease Risk Factors

- Male sex
- Family history of premature coronary artery disease (definite myocardial infarction or sudden death before age 55 in a parent or sibling)
- Cigarette smoking (currently smokes more than 10 cigarettes per day)
- Hypertension
- Low concentration of HDL cholesterol (below 35 mg/dl, confirmed by repeat measurement)
- Diabetes mellitus
- History of definite cerebrovascular or occlusive peripheral vascular disease
- Severe obesity (≥30% overweight)

Adapted with permission from *Arch Intern Med.*[5]

PATIENT SELECTION AND TREATMENT OF HYPERCHOLESTEROLEMIA

Once a lipoprotein analysis has been obtained, the LDL cholesterol level becomes the focus of interest. Levels of LDL cholesterol should be confirmed by 2 determinations separated by 1 to 8 weeks. Levels >160 mg/dl are considered high, those <130 mg/dl are normal, and those between 130 and 159 mg/dl are borderline (Table III). Patients who have high LDL cholesterol should undergo more intensive evaluation to establish, where possible, a genetic cause for the cholesterol elevation and to rule out other diseases that may be secondary causes of hypercholesterolemia (Table IV).

According to the guidelines, patients with LDL levels in the high range, as well as those with levels in the borderline range who also have established vascular disease or 2 other risk factors, are candidates for more intensive dietary therapy. Although the first phase of the diet is the same as that recommended for persons in the normal category, instruction and monitoring are applied more vigorously. Failure to lower LDL cholesterol to levels <160 mg/dl may lead to a more restricted dietary program (cholesterol intake <200 mg/day and saturated fat intake <7% of calories; Table V).[7]

Patients who cannot reduce LDL cholesterol levels to at least 190 mg/dl and who have no other risk factors, as well as those with established vascular disease or 2 risk factors and LDL levels >160 mg/dl, are candidates for drug therapy (Table VI). These thresholds for drug therapy were purposely set higher than those for diet therapy to avoid overprescription of drugs. Again, depending on the age and physical condition of the patient and the particular drug selected, considerable room has been left for physician discretion in the choice of treatment.

As a general statement, the committee ranked as first-choice drugs only those agents shown to lower not only LDL cholesterol, but also coronary artery disease risk. At

TABLE V Diet Recommended by National Cholesterol Education Program/American Heart Association*

	Estimated Current U.S. Adult Diet (% of Daily Calories)	Step 1	Step 2	Lipoprotein Effects	
				LDL	HDL
Total fat	35–40	<30%	<30%	Decrease	No change
Saturated fat	15	<10%	<7%	Decrease	No change
Polyunsaturated fat	7	10%	10%	Decrease	Decrease
Monounsaturated fat	16	10%	10%	Decrease	No change
Carbohydrate	40	50–60%	50–60%	No change	? Decrease
Protein	40	10–20%	10–20%	No change	No change
Cholesterol	500 mg/day	<300 mg/day	<200 mg/day	Decrease	? Decrease

* Current United States intake is contrasted with composition of recommended diets. Recommended diets are prescribed in 2 stages, with the second stage including further limitations in saturated fat and cholesterol intake.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.
Adapted with permission from *DAMON CLINICAL LABORATORIES.*[7]

the time of the report, only cholestyramine, colestipol and niacin qualified for this category. After the report was released, gemfibrozil was found to reduce the incidence of cardiovascular disease in the Helsinki Heart Study.[4] Consequently, many observers now believe that gemfibrozil should also be considered a first-choice agent, even though its ability to lower LDL is more limited and more erratic than that of the other first-line drugs.

RESPONSE TO THE GUIDELINES

Editorial commentary and physician and public interest suggest that these guidelines have had a major impact and, in general, have gained widespread acceptance, although such responses are difficult to quantify. At the very least, the recommendations have defined the minimum steps physicians should be expected to take in managing patients with hypercholesterolemia.

TABLE VI Recommended Lipid-Lowering Drugs

Drug	% LDL Cholesterol Lowering	Other Lipoprotein Effects	Reduces CAD Risk	Adverse Effects	Special Issues	Dose
Bile acid sequestrants (cholestyramine, colestipol)	15–25	Raises VLDL and triglycerides in some patients	Yes	Nausea, bloating, constipation, decreased absorption of other drugs	Provided as a bulky powder: adherence requires careful patient instruction	4–24 g/day (cholestyramine), 5–30 g/day (colestipol); given 2–3 times per day
Nicotinic acid	15–20	Raises HDL: lowers TG	Yes	Flushing, hyperuricemia, hyperglycemia, elevated LFTs, acanthosis nigricans	May be obtained as niacin without prescription; therapy requires physician supervision	Usually up to 30 g/day given 2–3 times per day
Gemfibrozil	5–10	Lowers TG: may raise HDL or LDL, or both, when TG decrease	Yes	Unclear; probably similar to clofibrate, i.e., abnormal LFTs, myositis (rare)	0	600 mg (2 300-mg capsules) given 2 times per day
Lovastatin	25–45	None	Not proved	Liver function abnormalities, myositis, (particularly when given with cyclosporine), (?) cataract (in animals only)	Monitor SGOT q 6–8 weeks; annual slit-lamp ocular exam	10–80 mg/day
Probucol	10–15	May lower HDL	Not proved	Prolongs QT interval; do not use if QT is prolonged or if there is ventricular irritability	Contraindicated if HDL 35 mg/dl; consider stopping if ratio of total cholesterol to HDL rises during therapy	10 g given 2 times per day

CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LFTs = liver function tests; SGOT = serum glutamic oxaloacetic transaminase; TG = triglycerides; VLDL = very low density lipoprotein.
Adapted with permission from *DAMON CLINICAL LABORATORIES.*[7]

Inevitably, the guidelines have engendered some criticism and concern. The element of the guidelines that has generated perhaps more comment than any other is the emphasis on LDL cholesterol as the primary target of treatment and the lack of emphasis on total cholesterol, triglycerides and HDL cholesterol.

In its deliberations, the Adult Treatment Panel vigorously debated whether to use total cholesterol or LDL cholesterol as the primary target for intervention. Those supporting total cholesterol argued that it can be measured easily and is more familiar to practicing physicians. Those supporting the use of LDL cholesterol argued that it more precisely reflects risk and, because HDL cholesterol is necessary for its calculation, indirectly takes levels of the latter lipoprotein into account in determining the extent of therapeutic intervention needed. The panel ultimately agreed to use LDL as a focus for selecting therapy, but suggested that total cholesterol can be used as a "surrogate" measurement for following the response of LDL cholesterol once therapy has been firmly established.[5]

Since the report dealt with the management of high cholesterol, the panel did not break new ground in recommendations concerning high triglyceride levels. The report did, however, generally, endorse the recommendations of the National Institutes of Health Consensus Panel on Hypertriglyceridemia, which define triglyceride levels <250 mg/dl as normal, those between 250 and 499 mg/dl as borderline, and those >500 mg/dl as high.[5,8] However, the Adult Treatment Panel strongly suggested avoiding drug therapy for hypertriglyceridemia in the absence of a concomitantly high level of LDL, except in patients who have triglyceride levels >1,000 mg/dl and who are, as a result, at risk of developing pancreatitis.

The report has been perhaps most vigorously criticized for its failure to recommend universal screening of HDL levels. These criticisms have been based on several concerns, including the following:

1. A small portion of persons with total cholesterol levels <200 mg/dl will have HDL cholesterol levels <35 mg/dl and will, therefore, be at risk for coronary disease even though their total cholesterol levels are normal.[9]
2. The panel was inconsistent in considering HDL levels <35 mg/dl as a separate risk factor when levels of this lipoprotein were not to be determined for all persons.
3. As many as 70% of persons with total cholesterol levels <200 mg/dl who also have coronary disease may have HDL levels <40 mg/dl.[10]
4. HDL levels are excellent predictors of the risk of coronary disease.
5. The Helsinki Heart Study[4] found that the increase in HDL obtained with gemfibrozil lowered coronary artery disease risk independent of any lowering of LDL.

These commentaries stimulated a response from the members of the panel reaffirming the report's approach to HDL.[11] The panel's justification for its approach included (1) the relatively small increase in risk in the lower cholesterol ranges, (2) the lack of widespread clinical trial evidence of the benefit of drug-induced isolated increases in HDL, and (3) the expense of obtaining routine determinations of HDL for all persons screened.

IMPLICATIONS FOR CLINICAL PRACTICE

Beyond the changes in cholesterol intervention hoped to be generated by these guidelines, the recommendations are likely to have other important effects. An increase in public awareness is almost inevitable and, in fact, is already becoming evident. This response, in turn, will lead to increased public expectations for cholesterol-related services. Depending on the rate of growth and demand, available resources may be strained. Because the guidelines lean so heavily on dietary intervention, dietary counseling services from physicians, registered dietitians and others are likely to increase substantially. Greater physician proficiency in the use of lipid-lowering drugs will be required as well. Because other risk factor interventions may also frequently be necessary, greater general proficiency in preventive medicine skills will be needed. Physicians and patients alike will expect lipid and lipoprotein determinations to be more accurate, more precise and less expensive.

In the long-term, of course, whatever temporary dislocations these guidelines engender should and will be corrected. Moreover, the widespread application of the guidelines promises to lead to a substantial reduction in the incidence of coronary atherosclerosis among the population in the United States.

REFERENCES

1. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results: II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA 1984;251:365–374.*

2. Blankenhorn DM, Nessim SA, Johnson RL, Sanmarco ME, Azen SP, Cashin-Hemphill L. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA 1987;257:3233–3240.*

3. Canner PL, Berge KG, Wenger NK, Stamler J, Friedman L, Prineas RJ, Friedewald W. Fifteen year mortality in coronary drug project patients: long-term benefits with niacin. *JACC 1986;8:1245–1255.*

4. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V, Mäenpää H, Mälkönen M, Mänttäri M, Norola S, Pasternack A, Pikkarainen J, Romo M, Sjöblom T, Nikkilä EA. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med 1987;317:1237–1245.*

5. Expert Panel. Report of the National Cholesterol Education Program. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *Arch Intern Med 1988;148:36–69.*

6. Friedewald WT, Levy RI, Frederickson DS. Estimation of the concentration of low density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem 1972;18:499–502.*

7. LaRosa JC. Lipoproteins: Their Role in Atherosclerosis and Its Prevention. Monograph for the Damon Corporation. *1988:13.*

8. NIH Consensus Conference: the treatment of hypertriglyceridemia. *JAMA 1984;251:1196–1200.*

9. LaRosa JC, Chambless LE, Criqui MH, Frantz ID, Glueck CJ, Heiss G, Morrison J. Patterns of dyslipoproteinemia in selected North American populations. *Circulation 1986;73:I-12–I-29.*

10. Abbott RD, Wilson PWF, Kannel WB, Castelli WP. High density lipoprotein cholesterol, total cholesterol screening and myocardial infarction: the Framingham Study. *Arteriosclerosis 1988;8:207–211.*

11. Grundy GM, Goodman DS, Rifkind BM, Cleeman JI. The place of HDL in cholesterol management. *Arch Intern Med 1989;149:505–510.*

At What Levels of Total Low- or High-Density Lipoprotein Cholesterol Should Diet/Drug Therapy be Initiated? European Guidelines

Gerd Assmann, MD

The control of coronary artery disease depends primarily on its prevention at an early stage. Researchers generally agree that early prevention depends on the elimination or treatment of known risk factors, among which hyperlipidemia occupies a central position. Two European Consensus Conferences have concluded that therapy of hyperlipidemia should always start with dietary counseling. First, subjects with body mass indexes (weight/height^2) >27 should lose weight. Second, the lipid-lowering diet should provide 55% of calories from carbohydrates; 10 to 15% from protein; and up to 30% from fat comprising 10% each of saturated, monounsaturated and polyunsaturated fatty acids; <300 mg/day cholesterol; 35 g/day of fiber derived largely from legumes and other vegetables; and fruit. Further reduction of fat consumption (to 20 to 25% of total energy) and of cholesterol (to <150 mg/day) may be attempted when patients respond inadequately to the standard diet. The goal of treatment is to minimize the risk of coronary artery disease and of pancreatitis. Where possible, a low-density lipoprotein cholesterol level of 135 mg/dl (3.5 mmol/liter) should be the goal in hypercholesterolemic patients with multiple or severe risk factors and a level of 155 mg/dl (4 mmol/liter) in the absence of other risk factors. Also, high-density lipoprotein cholesterol >35 mg/dl and triglycerides <200 mg/dl are considered important goals of treatment. Some patients with hyperlipidemia do not respond adequately to diet and correction of underlying causes; drug treatment should then be instituted, but careful attention to diet should be continued.

(Am J Cardiol 1990;65:11F–15F)

From the Institute of Arteriosclerosis Research; Institute of Clinical Chemistry and Laboratory Medicine, Central Laboratory, University of Münster, Münster, West Germany.

Address for reprints: Gerd Assmann, MD, Professor, Institut für Klinische Chemie und Laboratoriumsmedizin—Zentrallaboratorium, Universität Münster, Albert-Schweitzer-Str. 33, D-4400 Münster, West Germany.

In 1986 and 1987, scientists from 20 European countries convened to discuss the primary prevention of coronary artery disease (CAD) and the recognition and treatment of hyperlipidemia in adults.[1,2] These 2 consensus conferences adopted general principles for the prevention of CAD that are similar to those adopted by the U.S. National Institutes of Health Consensus Development Conference.[3,4] The European guidelines differ in some respects from the United States guidelines, however, and these distinctions are discussed.

CLASSIFICATION OF HYPERLIPIDEMIA

The European Consensus Conferences developed guidelines for risk assessment of CAD, as well as treatment regimens for each of 5 groups of hyperlipidemic patients (Tables I and II). The therapeutic goals identified for patients with hyperlipidemia depend to some extent on the presence or absence of other risk factors (Table III); plasma cholesterol and low-density lipoprotein (LDL) cholesterol target levels may be lower in persons with associated risk factors (Table IV).

Group A—mild hypercholesterolemia: Under the European guidelines, patients with cholesterol levels of 200 to 250 mg/dl and normal triglyceride levels (<200 mg/dl) are defined as having mild hypercholesterolemia. In the management of group A patients, as well as other hyperlipidemic patients, knowledge of cholesterol level alone is insufficient for the assessment of risk of myocardial infarction. Such an assessment must take into account other risk factors, including a family history of CAD, hypertension, diabetes, male gender, younger age, smoking, and low (<35 mg/dl) plasma levels of high-density lipoprotein (HDL) (Table II).

In general, the risk of CAD associated with mild hypercholesterolemia may be reduced by restriction of dietary cholesterol, nutritional counseling, weight loss and physical exercise, and reduction of other risk factors, if present. Drug treatment is rarely indicated for group A patients, unless they are at extremely high risk for CAD, as assessed by the presence and severity of other risk factors.

When lipid-lowering agents are indicated, a bile acid sequestrant may be prescribed in low doses. Alternatively, nicotinic acid, a fibrate derivative, or an hydroxymethylglutaryl coenzyme A reductase inhibitor may be given (Table V). The choice of drug will be influenced by variables such as patient age, level of HDL cholesterol, fibrinogen concentration, glucose tolerance and uric acid concentration.

TABLE I European Consensus Data—Classification of Hyperlipidemia

Group	Cholesterol Level (mg/dl)		Triglyceride Level (mg/dl)
A	200–250		<200 (normal)
B	250–300		<200 (normal)
C	<200		200–500
D	200–300		200–500
E	>300	and/or	>500

Adapted with permission from *Eur Heart J*.[1,2]

Group B—severe hypercholesterolemia: Patients with plasma cholesterol levels of 250 to 300 mg/dl and normal triglyceride levels (<200 mg/dl) are defined as having severe hypercholesterolemia. The cholesterol value alone does not precisely indicate which patients are at increased risk for CAD. In fact, many patients in group B (particularly premenopausal women and subjects with high levels of HDL cholesterol) do not necessarily have an increased risk of CAD.

Severe hypercholesterolemia due to elevation in LDL cholesterol (>155 mg/dl) should first be treated by restriction of dietary cholesterol plus a calorie-reduced diet for weight loss, if necessary. If the cholesterol level remains high after dietary modifications and weight loss, prescription of a lipid-lowering drug, particularly one that reduces LDL cholesterol, should be considered.

Group C—isolated hypertriglyceridemia: Patients with plasma cholesterol levels <200 mg/dl and triglyceride levels of 200 to 500 mg/dl are defined as having isolated hypertriglyceridemia. Underlying causes, such as obesity, excessive alcohol intake, diabetes, or a combination of these factors, should be identified. Correction of underlying causes often reduces the triglyceride level to a normal value.

A low-calorie diet should be prescribed if the person is overweight, because obesity leads to increased synthesis of very low density lipoproteins, thereby contributing to hypertriglyceridemia. A lipid-lowering diet should also be prescribed, and cholesterol and triglyceride levels should be monitored.

Drug treatment for group C patients is controversial. If a drug is prescribed, nicotinic acid or a fibrate derivative should be selected.

Group D—mixed hyperlipidemia: Patients with cholesterol levels of 200 to 300 mg/dl and triglyceride levels

TABLE II European Guidelines for Management of Hyperlipidemia

Group	Diagnostic Levels	Investigation	Management
A	Cholesterol 200–250 mg/dl (5.2–6.5 mmol/liter); triglyceride <200 mg/dl (<2.3 mmol/liter)	Assess overall risk of CAD, taking into account family history of CAD, hypertension, diabetes, male gender, younger age, smoking, low HDL cholesterol (>35 mg/dl [<0.9 mmol/liter])	Restrict food energy if overweight; give nutritional advice (lipid-lowering diet) and correct other risk factors if present; if LDL response inadequate, consider additional therapy in persons at very high risk; therapeutic goal—unless at overall risk, no follow-up; if at high risk, manage as Group B
B	Cholesterol 250–300 mg/dl (6.5–7.8 mmol/liter); triglyceride <200 mg/dl (<2.3 mmol/liter)	Assess overall risk of CAD as under A	Restrict food energy if overweight; prescribe lipid-lowering diet and monitor response and compliance; if cholesterol remains high, reinforce lipid-lowering diet; if this fails, consider drugs; correct other risk factors, if present
C	Cholesterol <200 mg/dl (5.2 mmol/liter); triglyceride 200–500 mg/dl (2.3–5.6 mmol/liter)	Seek underlying causes of hypertriglyceridemia (obesity, excessive alcohol intake, diuretics, β blockers, exogenous estrogens, diabetes)	Restrict dietary energy if overweight; deal with underlying causes if present; prescribe and monitor lipid-lowering diet; monitor cholesterol and triglyceride levels; correct other risk factors, if present
D	Cholesterol 200–300 mg/dl (5.2–7.8 mmol/liter); triglyceride 200–500 mg/dl (2.3–5.6 mmol/liter)	Assess overall risk of CAD as in A; seek underlying causes of hypertriglyceridemia as in C	Restrict dietary energy if overweight; deal with underlying causes of hypertriglyceridemia if present and proceed according to A or C; prescribe and monitor lipid-lowering diet; correct other risk factors, if present; if serum lipid response is inadequate and overall CAD risk is high, consider use of lipid-lowering drug
E	Cholesterol >300 mg/dl (7.8 mmol/liter^{-1}) and/or triglyceride >500 mg/dl (>5.6 mmol/liter)	Make full diagnosis on clinical and laboratory data	Dietary treatment and, commonly, drug therapy needed with ongoing supervision to maximize response; referral to specialist for diagnosis and initiation of therapy may be considered; particular attention is required for correction of other risk factors

CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
Adapted with the permission from *Eur Heart J*.[1,2]

TABLE III Factors Affecting Therapy of Hyperlipidemia

Modifiable Risk Factors	Other Factors
Hypertension	Family history of CAD or peripheral vascular disease
Cigarette smoking	Personal history of early onset CAD
Diabetes mellitus	Revascularization procedures
Obesity	Male gender
Low HDL cholesterol	Younger age

CAD = coronary artery disease; HDL = high-density lipoprotein.
Adapted with the permission of the *Eur Heart J.*[1,2]

TABLE IV Goals of Treatment for Hyperlipidemia

	No Other Marked Risk Factor Present		Other Marked or Multiple Risk Factors Present*	
	mg/dl	mmol/liter	mg/dl	mmol/liter
LDL cholesterol	155	4	135	3.5
Serum cholesterol	200–215	5.2–5.6	200	5.2
Serum triglyceride	200	2.3	200	2.3

* See Table III.
The relation between triglyceride levels and coronary artery disease is incompletely defined, and the value shown here is necessarily arbitrary at the current time. In the chylomicronemia syndrome and in severe familial hypertriglyceridemia, the goal of treatment is to minimize the risk of acute pancreatitis, which requires that triglyceride levels be reduced to <1,000 mg/dl (<11 mmol/liter), and preferably to <500 mg/dl (<5.6 mmol/liter).
LDL = low-density lipoprotein.
Adapted with the permission of the *Eur Heart J.*[1,2]

of 200 to 500 mg/dl are defined as having mixed hyperlipidemia. In treating these patients, the clinician should assess the overall risk of CAD and determine and treat underlying causes of hypertriglyceridemia. If the person is overweight, a low-calorie diet should be prescribed to reduce very low density lipoprotein synthesis. A lipid-lowering diet should also be prescribed, and plasma lipid levels monitored.

After the hypertriglyceridemia has been corrected, patients should receive treatment as recommended for those in groups A or B, depending on whether the cholesterol level is < or >250 mg/dl.

Drug treatment should be considered if the overall risk of CAD is high or if LDL or triglyceride levels are elevated, or both, despite prolonged efforts at dietary control. The drugs of choice vary according to the combination of cholesterol and triglyceride levels found in the patient (Table V). Any of 3 combinations of cholesterol or triglyceride levels may be present after dietary interventions. If the triglyceride level is elevated but the cholesterol level is within normal limits, nicotinic acid or a fibrate should be prescribed. If the cholesterol level is elevated but the triglyceride level is within normal limits, nicotinic acid, a bile acid sequestrant, a hydroxymethylglutaryl coenzyme A reductase inhibitor or a fibrate may be prescribed. If both triglyceride and cholesterol levels remain elevated, nicotonic acid, a fibrate, or a combination of lipid-lowering agents may be appropriate. Suggested regimens include a bile acid sequestrant plus a fibrate or, alternatively, a hydroxymethylglutaryl coenzyme A reductase inhibitor.

Group E—severe hypercholesterolemia or hypertriglyceridemia: Patients with cholesterol levels >300 mg/dl or triglyceride levels >500 mg/dl, or both, are defined as having severe hypercholesterolemia or hypertriglyceridemia, or both. Patients in this group should be cared for by a specialist in lipoprotein and lipid metabolism who should attempt to provide a precise diagnosis of the underlying metabolic defect and initiate treatment.

THERAPEUTIC GOALS

The therapeutic goal for a patient with hyperlipidemia is determined by the type and severity of CAD risk factors present (Table III). Modifiable risk factors include hypertension, cigarette smoking, diabetes, obesity and low levels of HDL cholesterol. If a modifiable risk factor is present, it should be eliminated or treated. Nonmodifiable risk factors include a family history of CAD or of peripheral vascular disease, a personal history of early-onset CAD or need for a revascularization procedure, male gender and younger age.

Whenever a hyperlipidemic person has pronounced or multiple risk factors, the therapeutic goal is affected. In a hyperlipidemic subject whose only risk factor is elevated cholesterol level, the therapeutic goals are to reduce the cholesterol level to <200 mg/dl and LDL level to <155 mg/dl (the National Institutes of Health Consensus Conference recommended an LDL level of <160 mg/dl and

TABLE V Choice of Lipid-Lowering Drugs

Group	Treatment
A	Drug treatment rarely indicated; if required for patients at extremely high CAD risk, selection as in Group B
B	Single-drug treatment considered for persistent LDL cholesterol elevation despite prolonged effort at dietary control: bile acid sequestrant (usually at low dosage), nicotinic acid, fibrate, or HMG-CoA reductase inhibitor
C	Drug treatment controversial; either nicotinic acid or fibrate
D	Drug treatment considered if LDL cholesterol or triglyceride elevation, or both, persist despite prolonged effort at dietary control: Cholesterol remains elevated, triglyceride within limits—nicotinic acid, fibrate, bile acid sequestrant, or HMG-CoA reductase inhibitor Triglyceride elevated, cholesterol within limits—nicotinic acid or fibrate Cholesterol and triglyceride elevated—nicotinic acid or fibrate, or fibrate plus bile acid sequestrant or HMG-CoA reductase inhibitor
E	Choice of drug treatment depends on diagnosis of primary lipid disorder: Familial hypercholesterolemia—bile acid sequestrant, HMG-CoA reductase inhibitor or nicotinic acid; for nonresponders use combination therapy—bile acid sequestrant with either nicotinic acid, fibrate, probucol, or HMG-CoA reductase inhibitor Remnant hyperlipidemia—fibrate or nicotinic acid Familial hypertriglyceridemia—nicotinic acid or fibrate Familial combined hyperlipidemia—drug treatment as under group D Primary chylomicronemia—drug treatment rarely indicated

CAD = coronary artery disease; HMG-CoA reductase = hydroxymethylglutaryl coenzyme A; LDL = low-density lipoprotein.
Adapted with the permission from *Eur Heart J.*[1,2]

TABLE VI U.S. Versus Europe on Guidelines—Major Differences

Lead Parameter	U.S. Guidelines—Total Cholesterol	European Guidelines—Total Cholesterol and Triglycerides
Cholesterol	200–239 mg/dl: borderline high, medical attention only if CHD or ≥2 risk factors present ≥240 mg/dl: high blood cholesterol, medical attention needed	Target and attention value: 200 mg/dl
Triglycerides	250–500 mg/dl: correct underlying cause, if present >500 mg/dl: medical attention needed	Target and attention value: 200 mg/dl In combination with low HDL cholesterol, "triglyceride appears to be an independent risk factor"
HDL cholesterol	<35 mg/dl considered a major risk factor; HDL measured as part of LDL cholesterol determination	"HDL cholesterol <35 mg/dl may be taken into account in deciding on the intensity with which hyperlipidemia should be treated"
LDL cholesterol	LDL cholesterol level is the basis for clinical decisions about dietary or drug therapy; 130–159 is borderline-high risk, ≥160 is high risk; borderline-high risk needs attention if linked with CHD or ≥2 risk factors present; minimal goal of treatment: <160 mg/dl or <130 mg/dl if CHD or ≥2 CHD risk factors present	Goal of treatment: 155 mg/dl, respectively; 135 mg/dl if other risk factors
Patient management	Guidelines on the basis of LDL cholesterol; HDL and other CHD risk factors used to modify initiation levels and goals of treatment; total cholesterol used to monitor response to diet	Guidelines on the basis of 5 treatment groups (A–E) (see Table V)
Drug treatment	Initiate if diet alone leaves LDL cholesterol ≥190 mg/dl, or if LDL cholesterol is 160–189 and CHD or ≥2 other risk factors present	Initiate if diet alone fails and target values not achieved; in groups A and C, if additional risk factors are present
	First choice: bile acid sequestrants and nicotinic acid; gemfibrozil particularly useful in patients with high LDL cholesterol who also have elevated triglycerides and low HDL cholesterol; lovastatin considered a highly effective new drug	Differentiates between pure hypercholesterolemia (first choice, bile acid sequestrants) and dyslipidemia (first choice, fibrate or nicotinic acid)
	NCEP 1989 recommendations: "When drug therapy is required for high LDL cholesterol levels in the presence of low HDL levels, cholesterol-lowering drugs that concomitantly raise HDL should be given first priority"	

CHD = coronary heart disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NCEP = National Cholesterol Education Program.
Information taken from the European Atherosclerosis Society[1,2] and the U.S. National Cholesterol Education Program.[4,5]

reduction of the triglyceride level to <200 mg/dl). In persons with pronounced or multiple risk factors, the therapeutic goal is the reduction of LDL to <135 mg/dl by way of an appropriate combination of dietary modifications and drug therapy (Table IV).

EUROPEAN VERSUS UNITED STATES GUIDELINES: SIMILARITIES AND DIFFERENCES

Both the European and the National Institutes of Health Consensus Conferences agreed that the relation between plasma cholesterol concentration and CAD is strong, as evidenced by data from a large number of studies, and that this relation is independent of the presence of other risk factors. When the elevated cholesterol concentration is attributed to a high level of LDL, elevated cholesterol has been found to have a causal role in atherosclerotic heart disease. Evidence has also shown that lowering an elevated plasma cholesterol level will reduce the risk of myocardial infarction.

The critical plasma cholesterol level appears to be 200 mg/dl—a premise strongly supported by the Multiple Risk Factor Intervention Trial. Mortality rates from CAD double as cholesterol levels increase from 200 to 260 mg/dl. Both the European and United States Consensus Conferences concurred, therefore, that the reduction of plasma cholesterol concentration to approximately 180 mg/dl in adults younger than age 30 years and to approximately 200 mg/dl in adults older than age 30 years should be encouraged.

On the other hand, the European Consensus Conference placed greater emphasis on the roles of high-density cholesterol and triglyceride concentrations than did the National Institutes of Health Conference. In particular, hypertriglyceridemia associated with low levels of HDL cholesterol was considered to be related to increased risk of CAD in many patients (Table VI).

POPULATION STRATEGY VERSUS HIGH-RISK STRATEGY

The European guidelines proposed 2 strategies for risk factor reduction. The population strategy is based on the recognition that, in almost all of the European countries, most CAD results from exposure of a large proportion of the population to moderately elevated levels of risk factors. Thus, this strategy seeks to promote health-oriented behaviors, (i.e., improved nutrition, smoking cessation and exercise) in the entire population so as to reduce the overall risk of CAD. Conversely, the high-risk strategy involves the widespread use of clinical and laboratory tests to identify the minority of persons within the population who are at a particularly high relative risk of CAD.

Alternative modes of identifying persons at high risk were suggested by the European strategy group. The first method, selective screening, involves targeted risk factor assessment of persons likely to have positive findings and

those in whom hyperlipidemia is likely to be particularly hazardous. Selection criteria for such screening include a positive family history of cardiovascular disease, particularly occurring at a relatively early age (<50 years); a family history of hyperlipidemia; the presence of xanthelasmas or corneal arcus in persons younger than age 40 years; obesity; diabetes mellitus; hypertension; smoking; and gout.

From the viewpoint of the community, selective screening is not sufficient as a means of reducing the incidence of CAD; a large proportion of persons at high risk would not be examined if assessment were confined to those having the characteristics listed. In regard to persons with 1 or more of these characteristics, however, risk factor assessment is recommended and positive findings may be anticipated in a substantial proportion of such persons.

The second method of identifying high-risk persons (called case finding, opportunistic screening or the health check) involves the sound practice of including risk factor assessment as part of a full clinical examination—e.g., at the first visit to a physician, during a medical examination for employment purposes (including entry into the armed services), or, when appropriate, during consultation for intercurrent medical problems. Over the course of several years, the goal is to recognize most people with levels of risk factors requiring treatment. By doing so in the context of the doctor-patient relation, compliance with advice and treatment is furthered. Case finding is best conducted at the primary health care level and in hospitals, since this affords an opportunity to reach as large a proportion of the population as possible. By extending the process over several years, the impact on clinical work load and laboratory costs is minimized; the high-risk strategy will, as is desirable, be introduced in concert with the population strategy.

The third method of identifying high-risk persons, general screening, involves a direct invitation to the public to undergo blood pressure measurement, laboratory tests or other investigations. In some countries, such activities are already underway for selected age groups, using existing screening facilities and trained primary health care personnel, who are following high-risk persons. In other countries, the abrupt institution of this strategy would create the problem of generating a very large caseload, possibly before the medical profession has had time to assimilate the implications of risk factor reduction at the clinical level. Screening should be performed only if provisions have been made for treatment and follow-up by medical practitioners.

The European study group suggested that the case-finding approach, coupled with selective "screening," currently provide the optimal means of detecting persons at particular risk in most countries. The population and individual strategies are considered complementary; implementation of each may enhance the effectiveness of the other. These 2 strategies represent different ways of bringing an essentially similar package of preventive measures to the population. Each has its strengths and limitations. Cigarette smoking, excess weight and unbalanced diets are so common that ongoing mass education will be needed to reach the large numbers of persons with such risk factors; this educational approach can and should be strongly reinforced in individual clinical practices. Similarly, undesirable or overtly high levels of serum cholesterol are exceedingly prevalent; in many countries, >50% of young and middle-aged persons have cholesterol levels >200 mg/dl (5.2 mmol/liter). On the other hand, the minority of the population with pronounced risk factors (e.g., moderate or severe hypertension, major genetic hyperlipidemia or marked obesity) require individual therapy in a clinical setting; for such persons, the moderate changes in health habits advocated by the population-based strategy will often be inadequate.

REFERENCES

1. Strategies for the prevention of coronary heart disease: a policy statement of the European Atherosclerosis Society. *Eur Heart J 1987;8:77–88.*

2. Recognition and management of hyperlipidaemia in adults: a policy statement of the European Atherosclerosis Society. *Eur Heart J 1988;9:571–600.*

3. NIH Consensus Development Conference: Lowering blood cholesterol to prevent heart disease. *JAMA 1985;253:2080–2086.*

4. Expert Panel. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *Arch Intern Med 1988;148:36–69.*

5. Grundy SM, Goodwin DS, Rifkind BM, Cleeman JI. The place of HDL in cholesterol management. A perspective from the National Cholesterol Education Program. *Arch Intern Med 1989;149:505–510.*

Lipid-Lowering Therapy After an Atherosclerotic Event*

William C. Roberts, MD

When considering lipid-lowering therapy (diet ± drug) for a patient who has had an atherosclerotic event, the following facts might be considered:

1. Whatever the levels of the serum (or plasma) total and low-density lipoprotein (LDL) cholesterol in the patient with an atherosclerotic event, they are too high for that particular patient.
2. The greatest risk factor for a subsequent atherosclerotic event is a previous atherosclerotic event.
3. The greatest danger period for a subsequent atherosclerotic event is the first 6 months after the previous atherosclerotic event.
4. The higher the serum total and LDL cholesterol levels, the greater the chance of a subsequent atherosclerotic event.
5. Portions of atherosclerotic plaques disappear ("reverse") when the total and LDL cholesterol levels are lowered, and when portions of plaques disappear the arterial lumens widen and blood flow to the organ supplied increases.
6. The greater the percent decrease in serum total and LDL cholesterol levels, the greater the disappearance (reversibility) of portions of atherosclerotic plaques.
7. Diet therapy alone (percent of calories from fat reduced from 40 to 30%) usually lowers the serum total and LDL cholesterol levels only about 10%, and a reduction of this magnitude probably causes little to no disappearance of portions of atherosclerotic plaques.
8. Most persons having atherosclerotic events have serum total cholesterol levels from 200 to 240 mg/dl (5.2 to 6.2 mmol/liter) and LDL cholesterol levels from 130 to 160 mg/dl (3.4 to 4.1 mmol/liter).

If the aforementioned 8 items are accepted as facts, is it appropriate to manage serum cholesterol levels in persons who have had atherosclerotic events in the same fashion as these levels are managed in persons who have not had atherosclerotic events? My answer is "no."

To better understand this answer it may be useful to summarize the therapeutic guidelines of the Adult Treatment Panel (29 members) of the National Cholesterol Education Program (slightly modified for simplicity), published in January 1988, for management of LDL cholesterol levels in persons aged 20 to 74 years in the USA.[1] The Panel had 3 therapeutic recommendations:

1. If the serum LDL cholesterol was 130 to <160 mg/dl and if definite coronary artery disease or 2 other risk factors were present, a low-fat, low-cholesterol diet should be prescribed. The "other risk factors" were male sex, history of acute myocardial infarction or sudden coronary death before 55 years of age in a parent or sibling, cigarette smoking (>10 cigarettes a day), systemic hypertension (not defined), serum high-density lipoprotein cholesterol <35 mg/dl (<0.9 mmol/liter), diabetes mellitus, history of cerebrovascular or peripheral arterial disease and severe obesity (≥30% overweight).
2. If the serum LDL cholesterol was 160 to 190 mg/dl (4.1 to 4.9 mmol/liter) in the absence of definite evidence of coronary artery disease and without the presence of 2 other risk factors, diet therapy should be prescribed.
3. If the LDL cholesterol was >190 mg/dl in the absence of definite evidence of coronary artery disease or 2 other risk factors, a lipid-lowering diet should be started and if the goal of <190 mg/dl was not obtained by diet in 6 months, then lipid-lowering drug therapy should be added.

Thus, the therapeutic recommendations of the National Cholesterol Education Program[1] are based primarily on the serum LDL cholesterol level and only secondarily on the presence of definite clinical evidence of coronary artery disease or other risk factors. The therapeutic recommendations are not greatly different for persons who have had definite coronary events (secondary prevention) and for those persons who have not (primary prevention). In my view, the occurrence of a coronary event (myocardial infarction, nonfatal cardiac arrest, angina pectoris associated with angiographically confirmed coronary arterial narrowing, and a positive exercise test result in the absence of symptoms of myocardial ischemia but in the presence of angiographically confirmed coronary arterial narrowing) should take precedence over the serum LDL cholesterol levels, and lipid-lowering therapy should be approached quite differently in the person who has had a coronary event compared with the person who has not.

Of persons residing in the USA who have not had an atherosclerotic event—and coronary events are by far the most common of them—slightly less than 50% will have one eventually if our lipid-consuming habits are not altered. Furthermore, of persons who have had 1 atherosclerotic event and survived, the chances are >90% that another atherosclerotic event will occur, and the chances

From the Pathology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

Address for reprints: William C. Roberts, MD, Pathology Branch, National Heart, Lung, and Blood Institute, Building 10, Room 2N258, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20892.

*This piece originally appeared in the September 15, 1989, From-the-Editor column in *The American Journal of Cardiology*.

also are >90% that the mode of death will be another atherosclerotic event. The major focus of management of a person who has had 1 atherosclerotic event is the prevention of a subsequent atherosclerotic event (secondary prevention).

The best deterrent to the occurrence of a subsequent atherosclerotic event is the lowering of the serum total and LDL cholesterol levels below the levels that were present at the time of the earlier atherosclerotic event. Even if the serum total cholesterol level was <200 mg/dl and the LDL cholesterol <130 mg/dl at the time of the first atherosclerotic event, these levels are too high for that patient. (Levels above these values are recognized to be too high for all persons irrespective of whether or not they have had atherosclerotic events.) Thus, irrespective of the actual serum total and LDL cholesterol levels at the time of or preceding an atherosclerotic event, the levels should be lower. If serum total and LDL cholesterol levels are lowered, the chances of a subsequent atherosclerotic event are lowered; the chances of dissolving (reversing) portions of atherosclerotic plaques and of increasing organ perfusion are increased and, consequently, the chances of longer survival are increased.

Because the initiation of a low-fat, low-cholesterol diet therapy usually causes only modest reduction in serum total and LDL cholesterol levels; because the chances of, and extent of, plaque reversibility appears to be roughly proportional to the extent of the reduction of the serum total and LDL cholesterol levels; because the chances of a subsequent atherosclerotic event decrease roughly proportional to the decrease in serum total and LDL cholesterol levels; and because the greatest danger of an atherosclerotic event is during the first 6-month period after a previous atherosclerotic event, maximal reduction in serum total and LDL cholesterol levels should occur as soon as possible after an atherosclerotic event. Maximal reduction is not best achieved by a 6-month trial of diet therapy. *It is best achieved by simultaneous initiation of both low-fat, low-cholesterol diet therapy and lipid-lowering drug therapy as soon as possible after the atherosclerotic event has occurred.* The goal is maximal reduction of both serum total and LDL cholesterol levels as soon as possible after the atherosclerotic event.

The drug or drugs chosen should be those that have the greatest capacity to lower the serum total and LDL cholesterol levels (Table I). In persons who have had no atherosclerotic events, a 1% reduction in serum total cholesterol yields at least a 2% reduction in the frequency of fatal coronary artery disease or nonfatal acute myocardial infarction.[2,3] There is no reason to believe that this 2 for 1 principle is inapplicable to persons who have had atherosclerotic events. The combination of a 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor (e.g., lovastatin) and a bile-acid sequestrant (e.g., cholestyramine, colestipol) have the capability of lowering the serum LDL cholesterol by 50%,[4] and theoretically this degree of reduction before an atherosclerotic event could eliminate the possibility of an atherosclerotic event. For those persons who have had an atherosclerotic event, it is reasonable to believe that a 50% reduction in serum LDL cholesterol would substantially decrease the chances of a subsequent atherosclerotic event.

TABLE I Maximal Recommended Daily Doses of "Lipid-Lowering" Drugs Presently Available in the USA and Their Average Effects on Serum Lipids

Drug	Daily Dose (g)	Daily Dose (mg)	Effects on Serum Lipids‖ TC	LDL	HDL	TG
Colestipol	30	30,000	↓18%	↓24%	↑6%	↑10%
Cholestyramine	24*	24,000	↓18%	↓24%	↑6%	↑10%
Nicotinic acid	3†‡	3,000†‡	↓20%	↓25%	↑10%	↓25%
Gemfibrozil	1.2†	1,200†	↓11%	↓12%	↑15%	↓40%
Probucol	1†‡	1,000†‡	↓10%	↓10%	↓23%	↓3%
Lovastatin	0.08§	80§	↓34%	↓42%	↑10%	↓25%

* Each gram of regular Questran contains 0.44 g of cholestyramine and each gram of Questran light (nutrasweet) contains 0.86 g of cholestyramine.
† This dose also is the usual dose.
‡ This dose can be increased but side effects increase considerably.
§ About 70% of the nearly 1.0 million persons in the USA now receiving lovastatin take only 20 mg a day (1 tablet). This is the only drug of the 6 that is a once-a-day medicine when taken in 20- or 40-mg dosage.
‖ These average values were obtained from several studies.[2-19] The averages assume that the study subjects are also on a lipid-lowering diet.
HDL = high density lipoprotein; LDL = low-density lipoprotein; TC = total cholesterol; TG = triglyceride.

Opponents of the viewpoint that simultaneous lipid-lowering diet and drug therapy should be initiated soon after an atherosclerotic event irrespective of the actual serum total and LDL cholesterol levels (assuming that secondary causes of hypercholesterolemia have been ruled out and that there are no contraindications to drug therapy) might argue that lipid-lowering drugs are expensive and that they have real or potential toxic effects. Yes, these drugs are expensive, but coronary artery disease is an expensive disease. It occurs because most of us eat expensive foods. Coronary angioplasty is an expensive procedure (each about $10,000) and about 200,000 were performed in the USA in 1988. Coronary bypass is an even more expensive procedure (each about $30,000) and about 250,000 of these operations were performed in the USA in 1988. Thirty percent of persons undergoing coronary angioplasty have restenosis at the angioplasty site within 6 months after the procedure. Although coronary bypass has proved to be highly beneficial, about 25% of persons having it increase both their serum cholesterol levels and their body weight during the first year after the procedure and both of these occurrences increase the chances of another atherosclerotic event.

In the USA an estimated 5.5 to 7.5 million persons have symptomatic myocardial ischemia and, therefore, the lipid-lowering drug cost potentially could be very expensive. If 5.5 million Americans with symptomatic myocardial ischemia each were treated with a single 20-mg tablet of lovastatin daily, then the total cost would be $2.75 billion a year ($1.50/tablet and $550/person/year). For this cost the average reduction in serum total cholesterol would be 17%, in LDL cholesterol 20%, in serum triglycerides 20%, and the serum high-density lipoprotein cholesterol would increase about 7%. A serum total cholesterol reduction of 17% should yield a sizable reduction in the frequency of subsequent coronary events. In contrast, the cost of performing 250,000 coronary bypasses each year currently is about $7.5 billion (nearly 3

times as much), and the cost of performing 200,000 coronary angioplasties each year currently is about $2.0 billion. The impact of treating several million persons who have had a coronary event with lipid-lowering drugs (+ lipid-lowering diet) might have an enormous impact on the nation's health.

Although 4 of the 6 drugs currently available (Table I) in the USA to lower the serum total and LDL cholesterol levels do cause an alteration in hepatic enzymes in 1 to 2% of recipients, these alterations are completely reversible when the drug is discontinued, and these hepatic enzyme alterations may not occur on another trial of the same drug. Rhabdomyolysis occurs in about 1 in 5,000 persons who receive lovastatin and are not concomitantly receiving cyclosporine. The operative procedures (angioplasty and bypass) designed to increase myocardial blood flow also, of course, have their "toxic" effects including death. The greatest danger for a person who has had a coronary event, however, is not a toxic effect from a drug or a complication of a coronary procedure or operation, it is the occurrence of another coronary event. The prevention of another coronary event should be the major thrust of therapy for those who have had an earlier event.

In my view, virtually all persons who have had coronary events would benefit by combined diet and drug lipid-lowering therapy including persons who have had coronary angioplasty and bypass procedures. Several studies are now in progress to definitely answer the question of the usefulness of lipid-lowering drugs in persons who have had coronary events. Enough data already are available, however, to support the view to increase the use of lipid-lowering drugs irrespective of serum total and LDL cholesterol levels in patients who have had atherosclerotic events.

REFERENCES

1. The Expert Panel. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *Arch Intern Med 1988;148:36–69.*

2. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. Lipid Research Clinics Program. *JAMA 1984;251:351–364.*

3. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. Lipid Research Clinics Program. *JAMA 1984;251:365–374.*

4. Grundy SM, Vega GL, Bilheimer DW. Influence of combined therapy with mevinolin and interruption of bile-acid reabsorption on low density lipoproteins in heterozygous familial hypercholesterolemia. *Ann Intern Med 1985;103:339–343.*

5. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V, Maenpaa H, Malkonen M, Manttari M, Norola S, Pasternack A, Pikkarainen J, Romo M, Sjoblom T, Nikkila EA. Helsinki heart study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med 1987;317:1237–1245.*

6. Manninen V, Elo MO, Frick MH, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Maenpaa H, Malkonen M, Manttari M, Norola S, Pasternack A, Pikkarainen J, Romo M, Sjoblom T, Nikkila EA. Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki heart study. *JAMA 1988;260:641–651.*

7. Atmeh RF, Stewart JM, Boag DE, Packard CJ, Lorimer AR, Shepherd J. The hypolipidemic action of probucol: a study of its effects on high and low density lipoproteins. *J Lipid Res 1983;24:588–595.*

8. Kesamiemi YA, Grundy SM. Influence of probucol on cholesterol and lipoprotein metabolism in man. *J Lipid Res 1984;25:780–790.*

9. Yamamoto A, Matsuzawa Y. Yokoyama S, Funahashi T, Yamamura T, Kishino B. Effects of probucol on xanthamata regression in familial hypercholesterolemia. *Am J Cardiol 1986;57:29–35.*

10. Kuo PT, Wilson AC, Kostis JB, Moreyra DE. Effects of combined probucol-colestipol treatment for familial hypercholesterolemia and coronary artery disease. *Am J Cardiol 1986;57:43H–48H.*

11. Sirtori CR, Sirtori M, Calabresi L, Franceschini G. Changes in high-density lipoprotein subfraction distribution and increased cholesteryl ester transfer after probucol. *Am J Cardiol 1988;62:73B–76B.*

12. The Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA 1975;231:360–381.*

13. Grundy SM, Mok HYI, Zech L, Berman M. Influence of nicotinic acid on metabolism of cholesterol and triglycerides in man. *J Lipid Res 1981;22:24–36.*

14. Havel RJ, Hunninghake DB, Illingworth DR, Lees RS, Stein EA, Tobert JA, Bacon SR, Bolognese JA, Frost PH, Lamkin GE, Lees AM, Leon AS, Gardner K, Johnson G, Mellies MJ, Rhymer PA, Tun P. Lovastatin (mevinolin) in the treatment of heterozygous familial hypercholesterolemia. A multicenter study. *Ann Intern Med 1987;107:609–615.*

15. Tikkanen MJ, Helve E, Jaattela A, Kaarsalo E, Lehtonen A, Malbecq W, Oksa H, Paakkonen P, Salmi J, Veharanta T, Viikari J, Aarynen M, and the Finnish Lovastatin Study Group. Comparison between lovastatin and gemfibrozil in the treatment of primary hypercholesterolemia: the Finnish multicenter study. *Am J Cardiol 1988;62:35J–43J.*

16. The Lovastatin Study Group III. A multicenter comparison of lovastatin and cholestyramine therapy for severe primary hypercholesterolemia. *JAMA 1988; 260:359–366.*

17. Grundy SM. Drug therapy in hyperlipidemia. Cholesterol and Coronary Disease. Reducing the risk. *J Lipid Res 1987;1:1–8.*

18. Bilheimer DW. Therapeutic control of hyperlipidemia in the prevention of coronary atherosclerosis: a review of results from recent clinical trials. *Am J Cardiol 1988;62:1J–9J.*

19. Blum CB, Levy RI. Current therapy for hypercholesterolemia. *JAMA 1989;261:3582–3587.*

Hydroxymethylglutaryl Coenzyme A Reductase Inhibitors as Monotherapy in the Treatment of Hypercholesterolemia

J. Findlay Walker, MD, and Deborah R. Shapiro, DrPH

A variety of double-blind studies have compared the efficacy of hydroxymethylglutaryl coenzyme A reductase inhibitors (lovastatin and simvastatin) with that of control agents (cholestyramine, fibrates and probucol) in patients with type IIA or IIB primary hypercholesterolemia. Results have shown that both lovastatin and simvastatin are more effective than the standard therapies with regard to reducing total and low-density lipoprotein cholesterol. Decreases in triglycerides and increases in high-density lipoprotein cholesterol were generally greater with fibrates. Ongoing studies are assessing the benefits of lovastatin and simvastatin in reducing the incidence of mortality from coronary artery disease, as well as causing regression of coronary atheroma.

(Am J Cardiol 1990;65:19F–22F)

From Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey.

Address for reprints: J. Findlay Walker, MD, Merck Sharp & Dohme Research Laboratories, Sumney Town Pike, West Point Building 35-7, West Point, Pennsylvania 09486.

Until recently, the standard therapies available for the treatment of hyperlipoproteinemia, especially primary hypercholesterolemia, have been relatively limited both in number and in therapeutic usefulness. In general, the more effective agents have been poorly tolerated, whereas the better-tolerated agents have had very limited efficacy. To some extent, at least, the limitations of the available therapies have been responsible for the failure of the medical community to adopt vigorous therapeutic strategies for the modification of lipid abnormalities, which have been recognized as cardiovascular risk factors for at least 30 years. During the past decade, agents have been described that lower serum cholesterol by inhibiting activity of the enzyme hydroxymethylglutaryl coenzyme A (HMG CoA) reductase, one of the early and rate-limiting enzymes in the body's intrinsic synthesis of cholesterol. The biosynthetic pathway is summarized in Figure 1.[1] Because most cholesterol in the body derives from intrinsic synthesis, not dietary intake, this was considered to be a desirable and specific target for therapeutic intervention.

Among the HMG CoA reductase inhibitors, lovastatin and simvastatin have each been approved for marketing in a number of countries. Lovastatin is marketed in the United States, Canada, Germany and Finland, among others, while simvastatin has been released in Sweden, the United Kingdom, The Netherlands, France and Italy. Pravastatin is in the late stages of development, but is not yet marketed, whereas fluvastatin is undergoing early clinical studies.

This article briefly reviews information on the comparative efficacy of lovastatin, simvastatin and standard therapy, based on clinical studies performed as part of the manufacturer's drug development programs.

PATIENT POPULATIONS AND STUDY DESIGN

Patients involved in these clinical programs had primary hypercholesterolemia of the IIA or IIB phenotype, with total cholesterol levels, on dietary therapy, >240 mg/dl, and low-density lipoprotein cholesterol levels >165 mg/dl. The subjects had undergone a washout period from previous drug therapy, followed by dietary therapy for at least 4 weeks, before randomization.

In studies conducted in the United States, a central laboratory was used for all lipid and other biochemical tests. In multinational studies in other countries, a central laboratory was not feasible, in general, but care was taken to assure the quality of the methods used; wherever possible, Centers for Disease Control standardization, or an equivalent, was ensured.

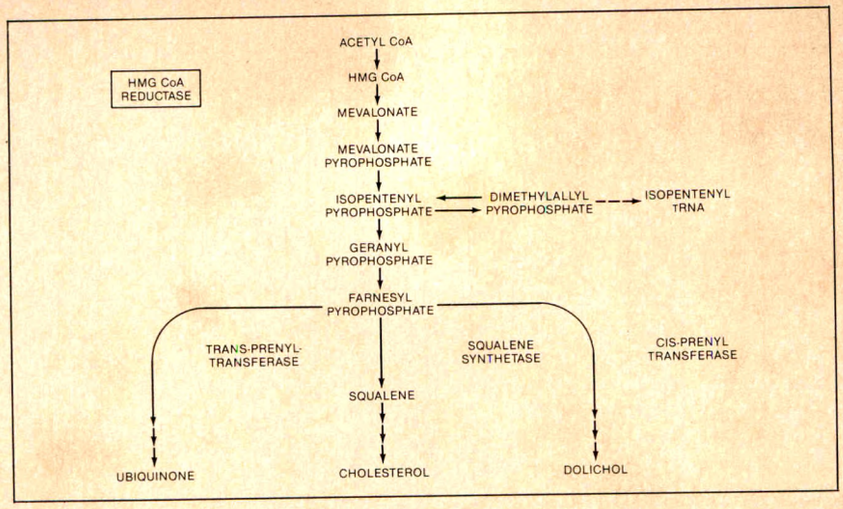


FIGURE 1. Cholesterol biosynthetic pathway. HMG CoA = hydroxymethylglutaryl coenzyme A. (Reprinted with permission from *Am J Cardiol.*[1])

TABLE I Numbers of Patients in Comparative Studies

Study	No. of Pts.
Lovastatin vs placebo (familial hypercholesterolemia)	101
Lovastatin vs placebo (nonfamilial hypercholesterolemia)	101
Lovastatin vs cholestyramine	264
Lovastatin vs probucol	290
Lovastatin vs gemfibrozil	334
Simvastatin vs placebo (familial and nonfamilial hypercholesterolemia)	416
Simvastatin vs cholestyramine*	516
Simvastatin vs probucol	243
Simvastatin vs gemfibrozil	290
Simvastatin vs bezafibrate	232

* Two protocols.

All direct comparative studies were double-blind, with the exception of comparisons to cholestyramine, for which there is no easily available placebo. The double-blind, comparative periods of the studies lasted 6 to 8 weeks when the comparative agent was placebo and 12 to 14 weeks when active control agents were used. These periods were followed by long-term open extensions. Doses of lovastatin ranged from 20 to 80 mg, given either as a single dose in the evening or twice daily. Simvastatin was generally given in doses of 10 to 40 mg once daily in the evening. Comparative agents were given according to the recommendations of the respective manufacturers: cholestyramine[2]* at a dose of 12 g twice daily (or the maximal dose tolerated by the patient), probucol[3,4] at 500 mg twice daily, gemfibrozil at 600 mg twice daily[5]* and bezafibrate at 200 mg 3 times daily.*

RESULTS

The numbers of patients treated in comparative studies with lovastatin and simvastatin are listed in Table I. Overall, in both programs, >60% of patients had familial hypercholesterolemia. Approximately 40% of the subjects had a history of ischemic heart disease.

Tables II and III list the results of the studies in terms of effects on total cholesterol, low- and high-density lipoprotein cholesterol, and the ratio of low- to high-density cholesterol for lovastatin and simvastatin, respectively. Both lovastatin and simvastatin were significantly more effective than were the control agents in terms of decreasing total and low-density lipoprotein cholesterol. Modest

* Data on file, Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey.

TABLE II Percent Changes in Lipid Variables—Comparative Studies with Lovastatin

Treatment Regimen	Total (%)	LDL (%)	HDL (%)	LDL/HDL (%)
Lovastatin 20 mg*	−16 to −22	−18 to −25	+6 to +13	−25 to −28
Lovastatin 40 mg	−22 to −27	−26 to −32	+5 to +13	−27 to −38
Lovastatin 80 mg	−30 to −34	−37 to −42	+9 to +12	−42 to −45
Cholestyramine	−17	−23	+8	−27
Probucol	−10	−8	−23	+26
Gemfibrozil†	−11/−16	−13/−18	18/12	−24/−23

* Because the percentage change at a given dose sometimes differed across studies, a range of response is given, if applicable.
† The data from this study were analyzed in 2 strata: I—total cholesterol <300 mg/dl; II—total cholesterol ≥300 mg/dl. Responses are given for stratum I/stratum II.
HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; Total = total cholesterol.

TABLE III Percent Changes in Lipid Variables—Comparative Studies with Simvastatin

Treatment Regimen	Total (%)	LDL (%)	HDL (%)	LDL/HDL (%)
Simvastatin 10 mg*	−21	−27	+4 to +10	−27 to −32
Simvastatin 20 mg	−27 to −28	−32 to −35	+10 to +14	−36 to −40
Simvastatin 40 mg	−30 to −33	−40 to −41	+10 to +13	−45
Cholestyramine	−15 to −21	−21 tp −29	+8 to +9	−25 to −34
Probucol	−13	−8	−27	+31
Gemfibrozil†	−16/−16	−20/−18	17/14	−28/−22
Bezafibrate†	−17/−18	−20/−20	14/23	−25/−31

* Because the percentage change at a given dose sometimes differed across studies, a range of response is given, if applicable.
† The data from these studies were analyzed in 2 strata: I—total cholesterol <300 mg/dl; II—total cholesterol ≥300 mg/dl. Responses are given for stratum I/stratum II.
Abbreviations as in Table II.

increases in levels of high-density lipoprotein cholesterol were seen with all agents except probucol; in several instances, the increases seen with the fibrates were significantly greater than those observed with lovastatin or simvastatin.

Triglyceride levels are generally lowered to a greater extent by the fibrates than by HMG CoA reductase inhibitors. In the 2 studies reported here in which comparisons were made to gemfibrozil, that agent achieved reductions in triglycerides of 30 to 45%, compared with reductions of approximately 15% with lovastatin or simvastatin.[5]*

DISCUSSION

The therapeutic options available for the treatment of hypercholesterolemia have been somewhat limited either by relatively low degrees of efficacy or by poor tolerability. Cholestyramine, the first of the lipid-lowering agents shown to be effective in primary prevention of coronary events,[6] is poorly tolerated, especially at higher doses.[7] Its mechanism of action involves inhibition of enterohepatic recirculation of bile acids, with a subsequent increase in the activity of low-density lipoprotein receptors on the hepatic cell; this leads to increased uptake of low-density lipoprotein cholesterol from the plasma, for production of more bile acids. Consequently, plasma cholesterol levels decrease.[7]

Probucol acts by a mechanism that is poorly understood, but may involve enhanced non–receptor-mediated clearance of lipoproteins. It has also been reported to prevent oxidative modification of lipoprotein particles.[8] Most of the decrease in cholesterol levels seen with probucol is attributable to reductions in high-density lipoprotein cholesterol, which may reflect decreased synthesis of apolipoprotein A-I.[9]

The fibrates—gemfibrozil, bezafibrate and others—generally have a greater effect on triglyceride levels than on cholesterol, as confirmed in these studies. Their mechanisms of action are complex, but involve activation of lipoprotein lipase with subsequent enhancement of metabolism of triglyceride-rich lipoproteins. They may also inhibit hepatic synthesis of fatty acids. Gemfibrozil has been shown to be effective in the primary prevention of coronary events, in the Helsinki Heart Study.[10]

The HMG CoA reductase inhibitors have a well-defined mechanism of action, involving specific inhibition of a key regulatory enzyme in the cholesterol biosynthetic cascade. The subsequent decrease in intracellular cholesterol levels leads to enhancement of cellular low-density lipoprotein receptor activity, which increases the cell's uptake of low-density lipoprotein cholesterol from the plasma. Circulating cholesterol levels decrease as a result.

After oral administration and absorption, lovastatin and simvastatin undergo substantial first-pass extraction by the liver,[11] allowing relatively little active drug to enter the systemic circulation. Because the liver is one of the principal sites of cholesterol synthesis,[12] this first-pass extraction effectively means that the highest concentrations of active drug are found in the desirable target organ.

With their highly specific mechanism of action, and remarkable efficacy as previously described, these drugs are likely to be highly desirable additions to the available lipid-lowering agents. As described by Tobert et al[13] in this supplement, up to 5 years of experience and 2 years of market experience with lovastatin in large numbers of patients have revealed a good tolerability profile.

Studies are underway to document the benefit of these drugs in reducing coronary mortality, as well as in causing regression of coronary atheroma. As these programs come to fruition, the HMG CoA reductase inhibitors should emerge as a mainstay of hypocholesterolemic therapy.

* Data on file, Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey.

REFERENCES

1. Alberts AW. Discovery, biochemistry, and biology of lovastatin. *Am J Cardiol 1988;62:10J–15J.*

2. Lovastatin Study Group III. Therapeutic responses to lovastatin and cholestyramine therapy for severe primary hypercholesterolemia. *JAMA 1988;260:359–366.*

3. Lovastatin Study Group IV. A multicenter comparison of lovastatin and probucol in the therapy of severe primary hypercholesterolemia (abstr). *Arteriosclerosis 1988;8:587a.*

4. Simvastatin Multicenter Study Group II: Effects of simvastatin and probucol in hypercholesterolemia. *Am J Cardiol 1989;63:682–686.*

5. Tikkanen MJ, Helve E, Jäättelä A, Kaarsalo E, Lehtonen A, Malbecq W, Oksa H, Pääkkinen P, Salmi J, Veharanta T, Viikari J, Äärynen M, and the Finnish Lovastatin Study Group. Comparison between lovastatin and gemfibrozil in the treatment of primary hypercholesterolemia. The Finnish multicenter study. *Am J Cardiol 1988;62:35J–43J.*

6. Lipid Research Clinics Program. The Lipid Research Clinics Primary Prevention Trial results: I. Reduction in incidence of coronary heart disease. II. The relationship of reduction in the incidence of coronary heart disease to cholesterol lowering. *JAMA 1984;251:351–374.*

7. Brown MS, Goldstein JL. Drugs used in the treatment of hyperlipidemias. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. The Pharmacological Basis of Therapeutics. *New York: Macmillan, 1985;827–845.*

8. Steinberg D. Metabolism of lipoproteins and their role in the pathogenesis of atherosclerosis. *Atherosclerosis Rev 1988;18:1–23.*

9. Nestel PJ, Billington T. Effects of probucol on low-density lipoprotein removal and high-density lipoprotein synthesis. *Atherosclerosis 1981;38:203–209.*

10. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V, Maenpaa H, Malkonen M, Manttari M, Norola S, Pasternack A, Pikkarainen J, Romo M, Sjoblom T, Nikkila EA. Helsinki Heart Study. Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med 1987;317:1237–1245.*

11. Duggan DE, Chen IW, Bayne WF, Halpin RA, Duncan CA, Schwartz MS, Stubbs RJ, Vickers S. Physiological disposition of lovastatin. *Drug Metab Dispos 1989;166–173.*

12. Tunley SD, Dutschy JM. Cholesterol metabolism and excretion. In: Arias I, Pepper H, Schacter D, Shaforty DA, eds. The Liver, Biology and Pathology. *New York: Raven Press, 1982:467.*

13. Tobert JA, Shear CL, Chremos AN, Mantell GE. Clinical experience with lovastatin. *Am J Cardiol 1990;65:23F–26F.*

Clinical Experience with Lovastatin

Jonathan A. Tobert, MD, PhD, Charles L. Shear, DrPH,
Athanassios N. Chremos, MD, and Geraldine E. Mantell, MD

New information on the tolerability of lovastatin has emerged from an ongoing study of long-term therapy; preliminary results from a large, 48-week clinical trial; and spontaneous reports of adverse events observed during prescription use of the drug in the United States. As of June 1989, 744 patients had received lovastatin for an average duration of 3.6 years in the long-term study. Drug-attributable adverse events necessitated withdrawal of 17 patients (2.3%) from the study. These adverse effects were asymptomatic elevations of transaminases (10), skin rash (3), gastrointestinal symptoms (2), myopathy (1) and insomnia (1). No effect of lovastatin on the human lens was observed. In the 48-week study, 8,245 patients were randomized into 5 equal groups to receive placebo or lovastatin 20 or 40 mg once or twice daily on a double-blind basis. Only 3 cases of myopathy were observed, all in patients taking lovastatin 40 mg twice daily. The incidence of withdrawal from the study because of raised transaminases was approximately 0.1% in the placebo group vs 0.1, 0.7, 0.6 and 1.5% in patients taking lovastatin in doses of 20 mg once daily, 40 mg once daily, 20 mg twice daily and 40 mg twice daily, respectively. Lovastatin has been available in the United States since September 1987. By June 1989, the drug had been prescribed for approximately 1 million patients. Drug-attributable adverse events not observed in clinical trials (such as hypersensitivity reactions and symptomatic hepatitis) have been reported, but the incidence of each appears to be extremely low.

(Am J Cardiol 1990;65:23F–26F)

From the Department of Clinical Research, Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey, and West Point, Pennsylvania.

Address for reprints: Jonathan A. Tobert, MD, PhD, Merck Sharp & Dohme Research Laboratories, P.O. Box 2000—WBD-228, Rahway, New Jersey 07065-0914.

The efficacy of hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors in treating hypercholesterolemia has been abundantly demonstrated (see review by Walker et al in this supplement). Lovastatin, the first HMG CoA reductase inhibitor available for prescription use, was introduced in the United States in 1987, and subsequently in Canada, West Germany, Denmark, Finland, Norway, Spain, Portugal, and more than 20 other countries. Simvastatin, closely related to lovastatin and the second drug introduced in this class, is available in various European countries (including France, Italy, Great Britain, Holland, Belgium and Sweden). Several other inhibitors of HMG CoA reductase are under development, but these agents will not be considered here because they are not available for prescription (as of June 1989), and published reports on these drugs are sparse. This article focuses on lovastatin, because it is the only HMG CoA reductase inhibitor currently available in the United States.

The tolerability of lovastatin has been analyzed in several recent reviews.[1–3] This paper provides an update on this information, based on data from an ongoing study of long-term therapy; preliminary results from a large, 48-week study; and spontaneous reports of adverse events observed during prescription use of the drug in the United States.

LONG-TERM THERAPY STUDY

Most of the patients who participated in 4 multicenter, controlled trials of lovastatin[4–7] have continued taking the drug. Data gathered at 23 participating clinics (17 in the United States) through March 1988 (when the average duration of therapy was 2.5 years) have been presented previously.[3] As of June 1989, the mean duration of therapy was 3.6 years. The population studied is at very high risk of coronary disease; 60% have familial hypercholesterolemia, accounting for the very high baseline plasma cholesterol of 359 mg/dl. Coronary or peripheral atherosclerosis is present in 48% of the subjects, including 40% who have a history of angina, myocardial infarction, or both, and 20% who have undergone coronary bypass surgery or angioplasty. Doses of lovastatin have been titrated up to the maximum of 80 mg/day in 66% of the subjects, reflecting the severity of their hypercholesterolemia. For the same reason, approximately half the patients have taken concomitant lipid-lowering agents (usually bile acid sequestrants) either intermittently or on a long-term basis. The outcome in these patients as of June 1989 is summarized in Table I.

Sixty-two patients (8.3%) have been lost to follow-up. Therapy was discontinued in 17 patients (2.3%) because of drug-attributable adverse events, and in another 22

TABLE I Lovastatin Long-Term Adverse-Effect Study—Interim Data on Patients' Status Through June 1989

Patient Status	No. of Pts.	%
Entered study	744	100.0
Continuing	642	86.3
Lost to follow-up	62	8.3
Discontinued due to		
Drug-attributable adverse events	17	2.3
Other adverse events	22	3.0
Poor response	1	0.1
Total	744	100.0

patients (3.0%), including 15 who died, because of adverse events not likely to be related to lovastatin. The drug-attributable adverse events (i.e., those events considered to be probably causally related to lovastatin) are summarized in Table II. The most common cause of discontinuation of therapy was an asymptomatic increase in transaminases that persisted at levels >3 times the upper limit of normal. Since the previous report, presenting data obtained through March 1988,[3] 1 additional patient has discontinued therapy (after 2.9 years) because of raised transaminases, bringing the total to 10. Nine of the 10 patients (including this last patient) who discontinued because of raised transaminases first experienced a transaminase value >3 times the upper limit of normal within 48 weeks of starting lovastatin. In the only other patient to discontinue therapy because of drug-attributable adverse events since March 1988 a rash developed that disappeared when lovastatin was withdrawn and reappeared after it was readministered. All 17 patients withdrawn from treatment had no clinical sequelae after lovastatin was discontinued.

Of the 22 patients who discontinued therapy because of adverse events not likely to be related to lovastatin, 15 died. Acute coronary events accounted for 14 of these deaths and carcinoma of the pancreas for 1. Of the 14 patients who died from coronary events, 12 had previous coronary disease. The coronary death rate was therefore 11 per 1,000 per year among patients with previous coronary disease, vs only 1 per 1,000 per year among those who did not have coronary disease. Considering the high-risk status of the study population, these rates are low. Therapy in the remaining 7 patients was discontinued because of breast cancer, peripheral neuropathy, depression, deep-vein thrombosis, weight gain, impotence, and rash while taking placebo. All these events, except for impotence, had been reported previously.[3] As discussed in this earlier report,[3] conditions that are not uncommon must be expected to occur occasionally in a large patient population followed up for a long period of time. Thus, none of these single case events need be attributed to lovastatin.

TABLE II Lovastatin Long-Term Adverse-Effect Study—Interim Data on Patients Discontinuing Therapy Because of Drug-Attributable Adverse Events Through June 1989

Adverse Event	No. of Pts.	%
Raised transaminases	10	1.3
Rash	3	0.4
Gastrointestinal symptoms	2	0.3
Myopathy	1	0.1
Insomnia	1	0.1
Total	17	2.3

Because of early concerns that HMG CoA inhibitors might cause cataracts, ophthalmologic examinations have been an important part of the evaluation of the long-term safety of lovastatin. As of March 1988, when the average duration of therapy up to the latest available ophthalmologic examination was 19 months, the prevalence of lens opacities had increased by 1.2% from a baseline prevalence of 35.2%. This increase, however, was less than the 2.5% increase in prevalence expected on the basis of the aging of the study population, as previously discussed.[3] These data, although reassuring, are not compelling because of the subjectivity of slit-lamp examination for detecting small lens opacities,[8] and the lack of a control group. For example, because of this subjectivity, substantial but spurious shifts in prevalence have been noted in centers where new opthalmologists have assumed responsibility for the lens examinations. In studies initiated subsequently, these problems have been avoided by the inclusion of a control group and the use of more sophisticated quantitative techniques for assesssing the lens (see later). Nevertheless, this study has provided useful information on outcomes that are easier to assess and equally clinically relevant. First, no patient has been withdrawn from the study because of lens changes. Second, only 8 patients, all at least age 60 years, have required cataract surgery; 6 of these subjects had lens opacities at baseline. Although there is no control group in this study, senile cataracts are a common occurrence in the general population, so that 8 patients (3.0 per thousand patient years) receiving cataract surgery is not unexpected. Third, in addition to the patients who underwent cataract surgery, only 2 patients have experienced a decrease in visual acuity of 2 lines or more (a 1-line change is within the margin of error of measurement) in association with a new lens opacity. Thus, while its limitations should be taken into account, this long-term, on-going study has provided no evidence for an effect of lovastatin on the human lens. Nevertheless, annual slit-lamp examinations are currently recommended.[9]

The interim results of this long-term study again confirm the favorable adverse-effect profile of lovastatin; the 2.3% drug-attributable discontinuation rate after a mean of 3.6 years of therapy is very low. Also, the study provides no evidence for new adverse events appearing after prolonged use. Illingworth et al,[10] who studied a group of patients treated for up to 5 years, reached a similar conclusion.

PRELIMINARY DATA FROM 48-WEEK STUDY

Merck Sharp & Dohme Research Laboratories, in collaboration with 362 centers in the United States, has

conducted a double-blind study in which 8,245 patients (who had total plasma cholesterol concentrations of 240 to 300 mg/dl and were consuming lipid-lowering diets) were randomized to treatment for 48 weeks. The 5 treatment groups were assigned to receive either placebo or lovastatin in doses of 20 or 40 mg once daily, and 20 or 40 mg twice daily, respectively. Approximately 1,600 patients were randomized into each of the 5 groups and approximately 1,400 in each group completed the trial; the last patient completed the study in June 1989. Slit-lamp examinations were standardized using a new lens opacity rating system.[11] This study will be reported in detail in the future. The following brief preliminary data on hepatic and muscle effects are provided:

As of June 1989, the allocation code had not been unmasked for most patients. However, the treatment assignments of patients who discontinued therapy prematurely because of raised transaminases or myopathy have been unmasked, and limited preliminary data are available. (The study protocol specified that all patients with transaminases increasing to >3 times the upper limit of normal, confirmed by a repeat measurement within 1 week, were to be withdrawn from the trial.) Data from these patients are shown in Table III. (An additional 4 patients had increased transaminases probably attributable to liver diseases—specifically, gallstones, primary biliary cirrhosis, and 2 cases of viral hepatitis.) Only 4 cases of myopathy occurred, 3 in patients receiving lovastatin 40 mg twice daily. Myopathy is defined for this purpose as diffuse muscle pain or weakness, or both, not attributable to exercise and accompanied by an increase in creatine kinase to at least 10 times the upper limit of normal.[3] (One of these episodes was coincident with acute cholecystitis and may have been precipitated by reduced bile flow impairing the elimination of lovastatin, which is excreted predominantly in the bile.[12]) At 20 mg administered once daily, therapy in only 1 patient was discontinued because of raised transaminases, yielding the same incidence as in the placebo group. Even at the highest dose (40 mg twice daily) the incidence was only 1.5%—below the figure of 1.9% previously reported in studies in high-risk patients with severe hypercholesterolemia.[3,9] In the long-term clinical study, as previously indicated, 9 of the 10 patients who discontinued therapy because of raised transaminases had values >3 times the upper limit of normal within 48 weeks of starting therapy with lovastatin. Similarly, in clinical trials, myopathy during therapy with lovastatin has usually occurred within 48 weeks of starting therapy, although some late-appearing cases have been reported when gemfibrozil or niacin has been added to lovastatin therapy.[3] To confirm that 48 weeks is long enough to capture most cases of raised transaminases, a subset of approximately 1,000 patients in the 48-week study are continuing on the allocated medications for an additional 48 weeks.

The dose-response relationships listed in Table III are particularly significant in light of the distribution of prescribed dosages in the United States. Currently, 67% of patients are taking 20 mg/day; 27%, 40 mg/day; 4%, 60 mg/day; and 2%, 80 mg/day.* The preliminary data from this study, therefore, indicate that the dose currently prescribed most often (20 mg/day) is associated, in typical patients, with a risk of raised transaminases or myopathy estimated to be <1 in 1,000 in each case. (It is possible that the incidence could be higher in patients with more complicated medical histories who were excluded from this study. Also, concomitant therapy with gemfibrozil or niacin, or immunosuppressant therapy including cyclosporine, is known to increase the risk of myopathy substantially[3]; such therapy was excluded from the study.) Monitoring of liver function tests and advising patients to report muscle symptoms are recommended.[9]

TABLE III Preliminary Data on Patients Discontinuing Lovastatin Because of Raised Transaminases and Myopathy in 48-Week Study (Approximately 1,500 Patients in Each Treatment Group)

Treatment	Raised Transaminases (%)	Myopathy (%)
Placebo	2 (0.1)*	0
Lovastatin (20 mg/day)	1 (0.1)	0
Lovastatin (40 mg/day)	10 (0.7)	1 (0.1)
Lovastatin (20 mg bid)	9 (0.6)	0
Lovastatin (40 mg bid)	20 (1.5)	3 (0.2)

* Values in parentheses indicate approximate incidence (%).

ADVERSE EVENTS DURING PRESCRIPTION USE IN THE UNITED STATES

Lovastatin has been available for prescription in the United States since September 1987. By June 1989, the drug had been prescribed for approximately 1 million patients. Spontaneous reports of adverse events provided by prescribing physicians or other health professionals have been carefully monitored to determine whether lovastatin is associated with rare adverse events not observed during clinical trials. Because it is impossible to know how many of the adverse effects that occurred are reported, the frequency of such events can be estimated only qualitatively.

The most recent analysis of spontaneous reports of adverse events during prescription use is based on reports received by a cutoff date of February 28, 1989. Approximately 900,000 patients had taken the drug up to this time. Of 13 deaths reported, 1 (discussed below) was thought to be drug related. Of the other deaths, 9 were caused by coronary heart disease (which must be expected in the population being treated), 1 by a cerebrovascular accident, 1 by leukemia and 1 by hepatic failure. This latter patient had undergone a bilateral nephrectomy due to polycystic kidney disease and had received multiple blood transfusions. Three weeks before the terminal illness, she had received intravenous antibiotics for a febrile episode. Although drug toxicity cannot be ruled out as a cause of hepatic failure, the history suggests that non-A/

*Joslyn A. Personal communication, 1989, based on unpublished Market Research Data from Pharmaceutical Data Services, Inc.

non-B hepatitis is more likely. The last case was a 65-year-old diabetic woman who experienced a frank rhabdomyolysis apparently caused by lovastatin, that precipitated acute renal failure. This patient, who had a history of depression, refused dialysis and consequently died. This case underscores the importance of physician and patient awareness of myopathy as an adverse effect of lovastatin; although rare, it can have serious sequelae.

Most of the nonfatal adverse events reported had been observed previously in clinical trials or are so common in the general population as to make a causal relationship to the drug seem unlikely (e.g., alopecia and depression). As previously reported,[3] there have been 10 reports of bleeding, increased prothrombin time, or both, in patients taking warfarin. Whether these events are caused by the drug is not clear, but prothrombin time should be monitored carefully in patients taking coumarin anticoagulant therapy concomitantly with lovastatin. The only new adverse events that were not observed in clinical trials and that appear related to lovastatin are serious hypersensitivity reactions and symptomatic hepatitis (as opposed to asymptomatic elevations of transaminases). As previously indicated, rashes have been observed during clinical trials with lovastatin and have occasionally required discontinuation of drug, but there have also been spontaneous reports of more serious hypersensitivity reactions during prescription use. These cases have had varying presentations, including anaphylaxis, arthralgia, lupus-like syndrome, angioedema, urticaria, hemolytic anemia, leukopenia and thrombocytopenia. Of these cases, 25 were considered serious, but all patients recovered after stopping lovastatin therapy. Although not all the cases were necessarily caused by lovastatin, a causal relationship with the drug is likely in at least some instances. Symptomatic hepatitis has also been reported. Of these cases, 8 to 21 (depending on the judgment of individual reviewers) were not associated with underlying liver disease or prescription of other drugs known to be hepatotoxic. Jaundice occurred in 4 of these patients, but all recovered or were in the process of recovery after lovastatin therapy was stopped. The liver function data in most of these reports are fragmentary, but it appears that both hepatocellular and cholestatic forms of hepatitis were observed. As with the hypersensitivity reactions, at least some of these 8 to 21 cases are believed to have occurred as the result of therapy with lovastatin. For both the serious hypersensitivity reactions and hepatitis, the number of reported cases is very low in relation to the very large number of patients taking the drug; this observation, combined with the fact that neither adverse effect was observed during the 48-week study in which more than 6,000 patients took lovastatin, indicates that the risk of both reactions is very low—certainly much less than 1 in 1,000.

Reports of myopathy occurring during prescription use of lovastatin have confirmed the findings of clinical trials; i.e., myopathy is clearly associated with concomitant gemfibrozil therapy, and less often with niacin or immunosuppressive therapy. In addition, as would be expected, the risk of myopathy appears to be greater when higher dosages of lovastatin are prescribed. There is also some evidence that patients with complicated medical histories may be at somewhat greater risk of developing myopathy.

CONCLUSIONS

Substantial experience in both clinical trials and prescription use has confirmed that lovastatin has a very satisfactory adverse-effect profile. The most important adverse events continue to be asymptomatic elevation of transaminases and myopathy, but new data reported herein indicate that the incidence of both events in typical patients is lower than previously reported in studies on high-risk patients with severe hypercholesterolemia. In typical patients taking lovastatin 20 mg once per day (the dose currently prescribed for approximately two-thirds of patients in routine clinical practice), the incidence of drug discontinuation due to raised transaminases or myopathy appears to be <0.1%.

REFERENCES

1. Grundy SM. HMG-CoA reductase inhibitors for treatment of hypercholesterolemia. *N Engl J Med 1988;319:24–33.*

2. Henwood JM, Heel RC. Lovastatin: a preliminary review of its pharmacodynamic properties and therapeutic use in hyperlipidemia. *Drugs 1988;36:429–454.*

3. Tobert JA. Efficacy and long-term adverse effect pattern of lovastatin. *Am J Cardiol 1988;62:28J–34J.*

4. Lovastatin Study Group II. Therapeutic response to lovastatin (mevinolin) in nonfamilial hypercholesterolemia. *JAMA 1986;256:2829–2834.*

5. Havel RJ, Hunninghake DB, Illingworth DR, Lees RS, Stein EA, Tobert JA, Bacon SR, Bolognese JA, Frost PH, Lamkin GE, Lees AM, Leon AS, Gardner K, Johnson G, Mellies MJ, Rhymer PA, Tun P. A multicenter study of lovastatin (mevinolin) in the treatment of heterozygous familial hypercholesterolemia. *Ann Intern Med 1987;107:609–615.*

6. Lovastatin Study Group III. A multicenter comparison of lovastatin and cholestyramine therapy for severe primary hypercholesterolemia. *JAMA 1988;260:359–366.*

7. Lovastatin Study Group IV. A multicenter comparison of lovastatin and probucol in the therapy of severe primary hypercholesterolemia (abstr). *Arteriosclerosis 1988;8:587a.*

8. Tobert JA. New developments in lipid-lowering therapy: the role of inhibitors of HMG-CoA reductase. *Circulation 1987;76:534–538.*

9. MEVACOR (lovastatin, MSD), U.S. package circular, June 1989.

10. Illingworth DR, Bacon SP, Larsen KK. Long-term experience with HMG-CoA reductase inhibitors in the therapy of hypercholesterolemia. *Atherosclerosis Rev 1988;18:161–187.*

11. Laties A, Keates E, Lippa EA, Shear CL, Snavely DB, Tupy-Visich M, Chremos AN. Field test reliability of a new lens opacity rating system utilizing slit-lamp examination. *Lens Eye Tox Res 1989;6:443–464.*

12. Duggan DE, Chen I-W, Bayne WF, Halpin RA, Duncan CA, Schwartz MS, Stubbs RJ, Vickers S. The physiological disposition of lovastatin. *Drug Metab Dispos 1989;17:166–173.*

Clinical Benefits and Cost-Effectiveness of Lowering Serum Cholesterol Levels: The Case of Simvastatin and Cholestyramine in The Netherlands

Leon L. Martens, MA, Frans F.H. Rutten, PhD, D. William Erkelens, PhD, and Carl A.P.L. Ascoop, PhD

To assess the cost-effectiveness of cholesterol-reducing therapy with cholestyramine and simvastatin in the primary prevention of coronary artery disease in The Netherlands, a model of coronary artery disease incidence was used based on multivariate logistic risk functions from the Framingham study. For men with initial cholesterol levels of 8 mmol/liter, the cost per year of life saved of cholestyramine, expressed in Dutch guilders (NLG; 1 NLG = $0.50), ranges from approximately NLG 208,000 to NLG 483,000, depending on the patient's age at initiation of therapy. For simvastatin, cost-effectiveness ranges from NLG 46,000 to NLG 98,000 per year of life saved among this group of men. Similar differences between simvastatin and cholestyramine therapy prevail among women, although the costs per year of life saved for both agents are considerably higher. These results suggest that (1) simvastatin is substantially more cost effective than is cholestyramine; (2) simvastatin therapy compares favorably with other generally accepted medical practices, especially if treatment is initiated at an early age; and (3) as its long-term safety record becomes more established, simvastatin may become accepted as a drug of first choice in the treatment of persons with elevated serum cholesterol levels.

(Am J Cardiol 1990;65:27F–32F)

Findings from the Lipid Research Clinics Coronary Primary Prevention Trial[1] and the Helsinki Heart Study[2] provide strong evidence of the efficacy of cholesterol-reducing therapy in the primary prevention of coronary artery disease (CAD).

Hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors (lovastatin, simvastatin and pravastatin) are a new group of pharmacologic agents that produce dose-related reduction of serum cholesterol levels through inhibition of HMG CoA reductase, the rate-limiting enzyme of cholesterol synthesis. Recent clinical studies suggest that these agents may be more effective in lowering serum cholesterol levels and may be associated with fewer side effects than are older medications.[3,4] The HMG CoA reductase inhibitors may, therefore, represent a significant advance in the treatment of elevated cholesterol levels and the prevention of CAD.

Cholestyramine has been the leading lipid-lowering agent in The Netherlands for many years and has been recommended by the Dutch Cholesterol Consensus Conference of March 1987 as the drug of first choice in the treatment of elevated serum cholesterol levels.[5] Since simvastatin became available in The Netherlands in January 1989, a reevaluation of the recommended treatment for patients with hypercholesterolemia is in order. Thus, in the present study, we assessed the clinical benefits and cost-effectiveness of simvastatin and cholestyramine* in preventing CAD among men and women with elevated serum cholesterol levels.

METHODS

General model: To estimate the clinical benefits and cost-effectiveness of the 2 drugs, we first developed a model of coronary disease incidence and mortality in each future year of life among cohorts of persons of any given age, sex and cholesterol level. Combining this model with data on the effectiveness and cost of cholesterol-reducing therapy, as well as data on the cost of treating symptomatic CAD, we estimated the changes in lifetime CAD risk, life expectancy, and future medical care costs for given pretreatment cholesterol levels.

We calculated the cost-effectiveness of cholesterol-reducing therapy as the ratio of the net treatment costs

From the Institute for Medical Technology Assessment, Erasmus University, Rotterdam, The Netherlands; Institute for Medical Technology Assessment, Erasmus University, Rotterdam, The Netherlands/University of Limburg, Maastricht, The Netherlands; Department of Internal Medicine, University Hospital Utrecht, The Netherlands; and Sint Antonius Hospital, Nieuwegein, The Netherlands. This research was supported by a grant in aid from Merck & Co., Inc., Rahway, New Jersey.

Address for reprints: Leon L. Martens, MA, Institute for Medical Technology Assessment, Erasmus University, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands.

*Fibrates are only prescribed for combined hyperlipoproteinemias in The Netherlands, so we did not compare simvastatin with a fibrate.

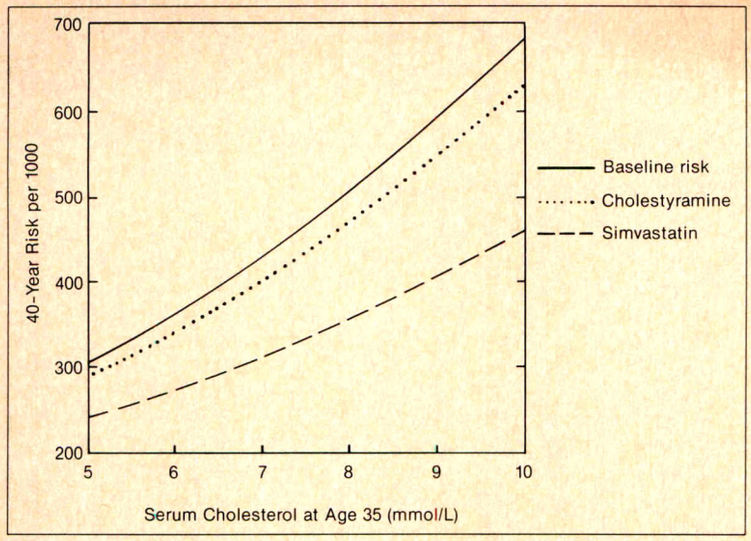


FIGURE 1. Forty-year risk of developing coronary artery disease, by cholesterol level at age 35 years, for Dutch men.

(i.e., cost of therapy minus any savings in the cost of treating symptomatic CAD) to the net change in life expectancy due to therapy. The net change in life expectancy for a cohort of any given age and gender was calculated as the discounted sum of the changes in the proportion of persons remaining alive in each future year due to therapy. The net change in medical care costs was calculated similarly, as the discounted sum of the changes in annual medical care costs in each future year of life. Changes in life expectancy and treatment costs were discounted at a 5% annual rate. All costs were adjusted to reflect 1988 price levels.

A detailed description of this model, which is based on multivariate logistic risk functions from the Framingham Heart Study, can be found elsewhere.[6]

Effectiveness of cholesterol-reducing therapy: The reduction in serum cholesterol levels that would be achieved by cholestyramine therapy was estimated using the dose-response relationship between total serum cholesterol and the daily intake of packets of cholestyramine reported in the Lipid Research Clinics study.[1,7] We estimated that 3 packets of cholestyramine per day would lower serum cholesterol by 6.2%, calculating this change as a reduction from on-diet baseline cholesterol levels. Based on the multicenter studies cited in the Marketing Authorization Application for Zocor®, we assumed that patients receiving one 20-mg tablet of simvastatin daily would have a 27% reduction from on-diet cholesterol levels.[8]

Cost of cholesterol-reducing therapy: According to the guidelines of the Dutch Cholesterol Consensus Conference,[5] dietary therapy should be prescribed for persons with serum cholesterol levels >6.5 mmol/liter. Treatment with a cholesterol-reducing medication should be initiated if, despite several months of dietary intervention, serum cholesterol remains >8 mmol/liter. We assumed that patients receiving a cholesterol-reducing diet would see their physicians twice each year and that, in order to monitor the effectiveness of therapy, cholesterol levels would be measured at each visit. We also assumed that

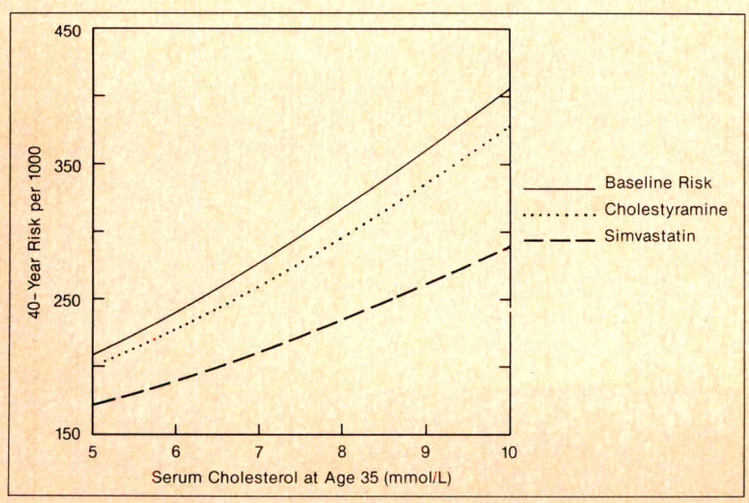


FIGURE 2. Forty-year risk of developing coronary artery disease, by cholesterol level at age 35, for Dutch women.

patients receiving hypolipidemic medications would visit their physicians 4 times per year to obtain new prescriptions, but that cholesterol measurement would be performed at only 2 of these visits. The marginal cost of cholesterol-reducing medication therefore consists of the drug cost, 2 additional physician visits, and, if applicable, the cost of monitoring for possible adverse effects of therapy.

We assumed that cholestyramine-treated patients would receive a typical regimen of 4-g packets 3 times per day; this regimen was based on the average prescribed dose of cholestyramine in The Netherlands according to International Marketing Statistics data (diagnostic index). Therefore, the total annual cost of adding therapy with cholestyramine to dietary therapy was estimated to be NLG 1,668.66 (1 NLG = $0.50).

Also, hypercholesterolemic patients who did not respond to diet and were eligible for simvastatin therapy were considered to receive a typical regimen of one 20-mg tablet of the drug each day. Furthermore, these patients would require additional laboratory testing to monitor liver function.* Therefore the total annual cost of therapy with simvastatin (added to dietary therapy) was estimated to be NLG 1,398.80.

RESULTS

Reduction in coronary artery disease risk: Estimates of the 40-year risk of CAD as a function of total serum cholesterol at age 35 are presented in Figures 1 and 2 for men and women, respectively. The baseline CAD risk is reported, as is the 40-year risk after initiation of cholesterol-reducing therapy with either cholestyramine or simvastatin at age 35. For both men and women at any serum cholesterol level, the reduction in CAD risk resulting from simvastatin therapy is substantially higher than that from therapy with cholestyramine. For instance, of 1,000 men with a serum cholesterol 8 mmol/liter at age 35, 505 will have a manifestation of CAD before age 75. Onset of CAD will be prevented among 38 of these men with cholestyramine therapy and among 151 men with simvastatin therapy. Both figures show that the benefits of cholesterol-reducing therapy increase, in both an absolute and a relative sense, as pretreatment cholesterol levels increase.

The average serum cholesterol level of 35-year-old Dutch men is approximately 5.5 mmol/liter. The results in Figure 1 show that almost 1 of every three 35-year-old Dutch men will experience some manifestation of CAD before age 75. The CAD risk among women is approximately two-thirds that of men with the same cholesterol level. Even after a 27% cholesterol reduction at age 35, the 40-year CAD risk among men remains >10% higher than that among women who have the same initial cholesterol level but are not subjected to cholesterol-reducing therapy.

*Further clinical studies have shown annual ophthalmic examinations to monitor the development of lens opacities to be superfluous. Hence, the recommendation to perform them has been deleted from the manufacturer's International Physician's Circular.

TABLE I Increase in Life Expectancy (Years) for Simvastatin and Cholestyramine Therapy Among Men and Women, by Cholesterol Level and Age at Initiation of Therapy

Age at Initiation of Therapy	Increase in Life Expectancy (Years) by Cholesterol Level at Initiation of Therapy for Simvastatin/Cholestyramine		
	7 mmol/liter	8 mmol/liter	9 mmol/liter
	Men		
35	1.23/ 0.33	1.75/ 0.48	2.44/0.67
40	1.00/ 0.27	1.40/ 0.38	1.92/0.52
45	0.77/ 0.20	1.05/ 0.28	1.41/0.38
50	0.54/ 0.14	0.72/ 0.19	0.94/0.25
55	0.33/ 0.09	0.44/ 0.11	0.56/0.15
60	0.18/ 0.05	0.24/ 0.06	0.30/0.08
65	0.08/ 0.02	0.11/ 0.03	0.14/0.04
70	0.03/<0.01	0.03/<0.01	0.04/0.01
	Women		
35	0.53/0.14	0.77/0.21	1.09/0.31
40	0.48/0.13	0.68/0.19	0.95/0.27
45	0.41/0.12	0.57/0.15	0.78/0.22
50	0.32/0.09	0.44/0.12	0.60/0.16
55	0.24/0.06	0.32/0.09	0.43/0.11
60	0.16/0.04	0.21/0.06	0.28/0.07
65	0.10/0.02	0.12/0.03	0.16/0.04
70	0.04/0.01	0.05/0.01	0.06/0.02

7 mmol/liter = 271 mg/dl; 8 mmol/liter = 310 mg/dl; 9 mmol/liter = 348 mg/dl.

Increase in life expectancy due to therapy: Table I lists undiscounted estimates for men and women of the increase in life expectancy with simvastatin and cholestyramine therapy by cholesterol level and age at onset of therapy. At all ages among both men and women, the gains in life expectancy with simvastatin are >3 times those with cholestyramine. For example, cholesterol-reducing therapy with simvastatin begun in 35-year-old men with initial cholesterol levels of 8 mmol/liter increases life expectancy by 1.75 years, whereas the gain in life expectancy from therapy with cholestyramine in a similar group of men is 0.48 years.

The gains in life expectancy for both simvastatin and cholestyramine increase with increasing pretreatment cholesterol levels. For example, for simvastatin therapy among men aged 35 years, the gain in life expectancy for those with pretreatment cholesterol levels of 9 mmol/liter is twice that for those with pretreatment cholesterol levels of 7 mmol/liter (2.44 vs 1.23 years).

For men and women at all pretreatment cholesterol levels, the gains in life expectancy for both therapies decrease as age at initiation of therapy increases. Among men with pretreatment cholesterol levels of 9 mmol/liter, e.g., simvastatin therapy begun at age 55 years produces one-fourth of the gain in life expectancy that would be achieved by starting therapy at age 35 years (0.56 vs 2.44).

Finally, for both simvastatin and cholestyramine, the gains in life expectancy among women are substantially lower than those among men for all pretreatment cholesterol levels and for all ages up to approximately 55 years. For example, simvastatin therapy begun at age 35 years

TABLE II Increase in Years of Life Free of Coronary Artery Disease for Simvastatin and Cholestyramine Therapy Among Men and Women, by Cholesterol Level and Age at Initiation of Therapy

Age at Initiation of Therapy	Increase in Years of Life Free of Coronary Artery Disease by Cholesterol Level at Initiation of Therapy for Simvastatin/Cholestyramine		
	7 mmol/liter	8 mmol/liter	9 mmol/liter
Men			
35	2.31/ 0.62	3.21/ 0.88	4.31/ 1.18
40	1.94/ 0.52	2.66/ 0.72	3.51/ 0.95
45	1.54/ 0.41	2.07/ 0.55	2.68/ 0.71
50	1.11/ 0.29	1.46/ 0.38	1.86/ 0.49
55	0.71/ 0.18	0.91/ 0.23	1.14/ 0.29
60	0.37/ 0.09	0.47/ 0.12	0.58/ 0.15
65	0.14/ 0.04	0.18/ 0.05	0.22/ 0.06
70	0.03/<0.01	0.03/<0.01	0.04/<0.01
Women			
35	0.90/ 0.23	1.19/ 0.31	1.53/ 0.40
40	0.82/ 0.21	1.07/ 0.28	1.38/ 0.36
45	0.70/ 0.18	0.91/ 0.24	1.16/ 0.30
50	0.56/ 0.14	0.72/ 0.18	0.91/ 0.24
55	0.40/ 0.10	0.51/ 0.13	0.64/ 0.16
60	0.24/ 0.06	0.31/ 0.08	0.38/ 0.10
65	0.11/ 0.03	0.14/ 0.04	0.17/ 0.04
70	0.02/<0.01	0.03/<0.01	0.04/<0.01

7 mmol/liter = 271 mg/dl; 8 mmol/liter = 310 mg/dl; 9 mmol/liter = 348 mg/dl.

among persons with pretreatment cholesterol levels of 8 mmol/liter results in a gain in life expectancy of 0.77 years for women compared with 1.75 years for men. Therapy begun between the ages of 60 and 70 years, however, yields similar results in life expectancy for men and women.

Increase in expected years of life free of coronary artery disease due to therapy: Table II reports undiscounted estimates for men and women of the gains in years of life free of CAD with simvastatin and cholestyramine therapy. The years of life gained free of CAD from either therapy are, for men and women of all ages and pretreatment cholesterol levels, considerably higher than the reported gains in life expectancy. Also, at all ages among both men and women, the gains in years of life free of CAD with simvastatin are almost >4 times those with cholestyramine.

The gains in expected years of life free of CAD for both therapies increase with increasing pretreatment cholesterol levels. For example, among men aged 35 years starting simvastatin therapy, the gain in number of years of life free of CAD for those with pretreatment cholesterol levels of 9 mmol/liter is almost twice that of those with pretreatment cholesterol levels of 7 mmol/liter (4.31 vs 2.31 years).

For men and women at all pretreatment cholesterol levels, the gain in years of life free of CAD with both simvastatin and cholestyramine decreases as age at initiation of therapy increases. Among men with pretreatment cholesterol levels of 9 mmol/liter, e.g., simvastatin therapy begun at age 55 years produces one-fourth of the gain in life expectancy that would be achieved by starting therapy at age 35 years (1.14 vs 4.31).

For both therapies, the estimated gains in years of life free of CAD among women are substantially lower than those among men, for all pretreatment cholesterol levels and for all ages up to approximately 60 years. For example, simvastatin therapy begun at age 35 years among persons with pretreatment cholesterol levels of 8 mmol/liter results in a gain in years of life free from CAD of 1.19 years for women compared with 3.21 years for men. Therapy begun between the ages of 65 and 70 years, however, yields similar results in life expectancy for men and women.

Cost-effectiveness of therapy: Figure 3 represents cost-effectiveness ratios (i.e., net direct costs per year of life saved) for cholestyramine and simvastatin for Dutch men between the ages of 35 and 60 years at initiation of therapy with pretreatment cholesterol levels of 7, 8 and 9 mmol/liter. Simvastatin is substantially more cost-effective in the treatment of elevated serum cholesterol than is cholestyramine. For men with initial cholesterol levels of 8 mmol/liter, the cost-effectiveness of cholestyramine ranges from approximately NLG 208,000 to NLG 483,000 per year of life saved, depending on age at initiation of therapy. For a similar group of men treated with simvastatin, cost-effectiveness ranges from NLG 46,000 to NLG 98,000 per year of life saved.

Figure 4 presents cost-effectiveness ratios for women. Although the cost-effectiveness of both agents is considerably less among women, simvastatin continues to be more cost-effective than cholestyramine. For example, among 50-year-old women with cholesterol levels of 8 mmol/liter, simvastatin therapy increases life expectancy at a cost of approximately NLG 128,000 per year of life saved, whereas the corresponding figure for cholestyramine is NLG 581,000.

Costs per year of life saved for both simvastatin and cholestyramine are substantially lower for persons with higher pretreatment levels of cholesterol. For a 40-year-old man with an initial cholesterol level of 7 mmol/liter, e.g., therapy with simvastatin increases life expectancy at a cost of approximately NLG 70,000 per year. The cost per year of life saved among those with an initial cholesterol level of 9 mmol/liter is NLG 30,000, however.

Cholesterol-reducing therapy in men is most cost-effective when initiated at an early age. For both simvastatin and cholestyramine, the cost per year of life saved is approximately twice as high when therapy is initiated at age 60 rather than at age 35 years.

Although therapy for women is most cost-effective when initiated between the ages of 45 and 55 years, the cost per year of life saved does not vary substantially when therapy is started between the ages of 35 and 60 years. For women with an initial cholesterol level of 8 mmol/liter, the cost per year of life saved ranges from NLG 128,000 to NLG 162,000.

CONCLUSION

Using a model of the incidence and prevalence of CAD in The Netherlands based on logistic risk functions

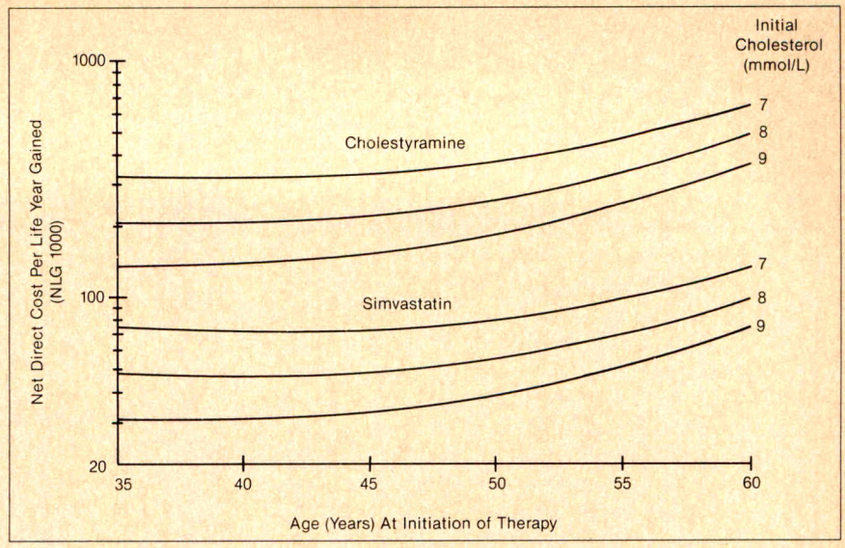


FIGURE 3. Cost-effectiveness of cholesterol-reducing therapy with simvastatin vs cholestyramine, by cholesterol level and age at initiation of therapy, among Dutch men. (1 NLG = $0.50.)

from the Framingham study, we have assessed the cost-effectiveness of cholesterol-reducing therapy with simvastatin and cholestyramine. Our results indicate that therapy with simvastatin is both substantially more effective and less expensive than therapy with cholestyramine. Although cholestyramine is not well tolerated by many patients, its long-term safety has been established by the Lipid Research Clinics Coronary Primary Prevention Trial.[1] When, in the course of time, the long-term safety of simvastatin becomes increasingly established, this agent may be accepted as a drug of first choice in the treatment of persons with elevated serum cholesterol levels.

Our results indicate that the cost per year of life saved among men rapidly increases when therapy is initiated at a later age. The identification of hypercholesterolemia and the subsequent initiation of treatment should, therefore, be accomplished at an early age. For women, the cost per year of life saved does not vary substantially with age when therapy is started between the ages of 35 and 60 years.

Our results confirm an inverse relation between the cost per year of life saved and the pretreatment cholesterol level, which provides an economic rationale for the Dutch Cholesterol Consensus Conference's recommendation to initiate drug treatment only above a certain level. From a clinical point of view, it is rational to decrease cholesterol levels in the entire population, since the relation between serum cholesterol and CAD mortality is continuous and graded.[9] Costs per year of life saved increase rapidly, however, with decreasing pretreatment cholesterol levels.

According to the guidelines of the Dutch Cholesterol Consensus Conference, drug treatment should be initiated when serum cholesterol levels remain >8 mmol/liter after several months of diet. When therapy is begun in 40-

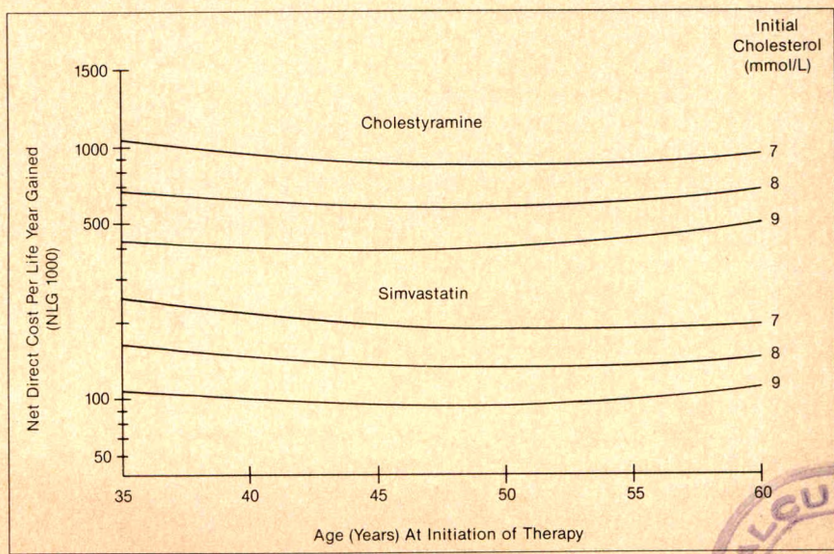


FIGURE 4. Cost-effectiveness of cholesterol-reducing therapy with simvastatin vs cholestyramine, by cholesterol level and age at initiation of therapy, among Dutch women. (1 NLG = $0.50.)

CALCUTTA CENTRAL LIBRARY UNIVERSITY

year-old men and 50-year-old women who have a pretreatment cholesterol level of 8 mmol/liter, cholestyramine increases life expectancy at a cost per year of life saved of NLG 210,000 and NLG 581,000, respectively. These cost-effectiveness ratios compare highly unfavorably with those of other health care programs in The Netherlands, such as screening for breast cancer,[10] intracoronary thrombolysis,[11] screening for cervical cancer,[12] heart transplantation,[13] the end-stage renal disease program[14] and liver transplantation,[15] the cost-effectiveness ratios of which are approximately NLG 10,000, NLG 8,000 to 25,000 (anterior and inferior infarction, respectively), NLG 24,000, NLG 52,000, NLG 54,000, and NLG 47,000 to 133,000. When therapy is begun among 40-year-old men with cholesterol levels of ≥8 mmol/liter, simvastatin gains life years at a cost of ≤NLG 46,000, which is well within the range of cost-effectiveness ratios of the aforementioned medical practices.

The cost per year of life saved with simvastatin therapy among women with a serum cholesterol level of 8 mmol/liter ranges from NLG 128,000 to NLG 162,000, depending on the age at which therapy is begun. These cost-effectiveness ratios compare unfavorably with those of the above-mentioned health care interventions in The Netherlands. Based on further analysis (which will not be presented in this report but is available from us on request), we recommend that cholesterol-reducing therapy for women in The Netherlands be limited to those with diabetes mellitus or severely elevated serum cholesterol levels.

Our results and conclusions have been obtained and inferred in the context of the Dutch health care system. Analysis has shown that the costs per year of life saved are very sensitive to the price of the drugs under consideration. Drug prices vary between countries, and so will the resulting cost-effectiveness ratios. Similarly, our conclusion that cholesterol reduction among women should be limited to those with diabetes mellitus or severely elevated cholesterol levels does not necessarily hold in countries other than The Netherlands.

We must also emphasize some of the methodologic limitations of our study. First, in estimating the benefits of cholesterol reduction, our study assumes that, after a 2-year time lag from the initiation of therapy in which no benefits are achieved, the CAD risk in persons whose cholesterol level has been lowered equals that of persons with naturally occurring lower cholesterol levels. Although preliminary calculations have shown that using Framingham risk functions under this assumption does not overestimate the benefits of cholesterol reduction, further analysis needs to be done.

Furthermore, the numbers presented in this report may underestimate the benefits and cost-effectiveness of cholesterol reduction. Serum cholesterol levels in persons show a considerable variation around an average level due to intraindividual biologic variations. The analytic variations in laboratory determinations of serum cholesterol further increase the variance in serum cholesterol values. The Dutch Cholesterol Consensus Conference, therefore, has advised clinicians to base their decision on whether to start cholesterol-reducing therapy on the average of 3 cholesterol determinations, which should be performed with several weeks between them.[5] The risk functions from the Framingham Heart Study, however, are based on a single cholesterol measurement, and, therefore, are likely to underestimate the relation between CAD incidence and a serum cholesterol level which is the average of 3 measurements. In the near future, we will report on algorithms we are currently developing to correct the logistic risk functions for the error in cholesterol measurement.

Acknowledgment: We express our appreciation to the Department of Epidemiology, Erasmus University, Rotterdam, for providing data from the Epidemiologic Preventive Study Zoetermeer, and to Joel Hay, Gerry Oster, Bryan Luce, M. Eugene Smith, Joseph Heyse and Patricia Finn for their helpful comments.

REFERENCES

1. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial Results: I. Reduction in incidence of coronary heart disease. *JAMA 1984;251:351–364.*

2. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V, Mäenpää H, Mälkönen M, Mänttäri M, Norola S, Pasternack A, Pikkarainen J, Romo M, Sjöblom T, Nikkilä EA. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med 1987;317:1237–1245.*

3. Lovastatin Study Group III. A multicenter comparison of lovastatin and cholestyramine therapy for severe primary hypercholesterolemia. *JAMA 1988; 260:359–366.*

4. Tobert JA. Efficacy and long-term adverse effect pattern of lovastatin. *Am J Cardiol 1988;62:1J–9J.*

5. Voorbereidingswerkgroep Cholesterolconsensus. Cholesterolconsensus: de stellingen toegelicht. *Hart Bull (suppl) 1987;1:3–11.*

6. Martens LL, Rutten FFH, Erkelens DW, Ascoop CAPL. Cost effectiveness of cholesterol-lowering therapy in The Netherlands: simvastatin versus cholestyramine. *Am J Med 1989;87:54S–58S.*

7. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial Results: II. The relationship of reduction in incidence of coronary heart disease to cholesterol-lowering. *JAMA 1984;251:365–374.*

8. Marketing Authorization Application for Zocor (simvastatin). Data on file at Merck Sharp & Dohme Research Laboratories, Blue Bell, PA, and at the Food and Drug Administration, Washington, D.C.

9. Martin MJ, Hulley SB, Browner WS, Kuller LH, Wenthworth D. Serum cholesterol, blood pressure, and mortality: implications from a cohort of 361,662 men. *Lancet 1986;2:933–936.*

10. Maas PJ van der, Ineveld BM van, Oortmarssen GJ van, Koning HJ de, Lubbe JThN, Habbema JDF, Birnie E, Geerts A, Bruyn AE de, Collette HJA, Rombach JJ, Verbeek ALM, Straatman H, Hendriks JACL, Heuvel WJA van den. De kosten en effecten van bevolkingsonderzoek op borstkanker. Interimrapport 1987. *Rotterdam: Instituut Maatschappelijke Gezondheidszorg, Erasmus Universiteit, 1987.*

11. Martens LL, Van Doorslaer EKA. Dealing with discounting: an application to the cost-effectiveness of intra-coronary thrombolysis with streptokinase. *Int J Tech Assess Hlth Care 1990;in press.*

12. Habbema JDF, Lubbe JThN, Agt HME van, Ballegooyen M van, Koopmanschap MA, Oortmarssen GJ van. Kosten en effecten van bevolkingsonderzoek op baarmoederhalskanker. *Rotterdam: Instituut Maatschappelijke Gezondheidszorg, Erasmus Universiteit, 1988.*

13. De Charro F, Bonsel GJ, Hout BA van. De kosten en effecten van harttransplantatie. Deelrapport 9: Eindrapport. *Rotterdam: Erasmus Universiteit, 1988.*

14. De Charro F. Kosten-effectiviteitsanalyse van het nierfunktievervangingsprogramma in Nederland. *Delft: Eburon, 1988.*

15. Bonsel GJ, Habbema JDF, Bot ML, Veer F van't, De Charro FT, Maas PJ van der. Een 'technology assessment' van levertransplantatie; een onderzoek naar het Groningse levertransplantatieprogramma van 1977–1987. *Ned Tijdschr Geneeskd 1989;133:1406–1414.*

Can Atherosclerotic Plaques Regress? Anatomic and Biochemical Evidence from Nonhuman Animal Models

Robert W. Wissler, PhD, MD, and Dragoslava Vesselinovitch, DVM, MS

For at least 60 years, spotty and poorly documented evidence has suggested that atherosclerotic disease in humans might be reversible. Little direct evidence was available until researchers demonstrated that rather advanced atherosclerotic lesions in experimental animals could show marked improvement after blood-lipid-reducing regimens that were often combined with other measures, such as increased ambient oxygen and estradiol therapy. In fact, this combination was used in this laboratory to produce one of the first effective regression studies in the rabbit model. In more recent studies in this laboratory, abundant evidence has been obtained that the advanced, eccentric, largely intimal lesions produced in the rhesus monkey are substantially reversible, and the much more inflammatory, concentric, and often transmural atheroarteritis induced by the same atherogenic ration in the cynomolgus monkeys is much more resistant to effective and beneficial regression. This unusual reaction appears to be due to the circulating immune complexes that participate in the pathogenesis of atherosclerosis in these cynomolgus monkeys, as well as possibly in a number of humans. The evidence for this phenomenon, as well as the varying effects of the lesions induced with contrasting food fats, is summarized in this presentation. Some of the time-related effects of varying interventions when the lesions are studied at 4-month intervals in rhesus and cynomolgus monkeys are also discussed. Other factors that may influence regression are also considered.

(Am J Cardiol 1990;65:33F–40F)

From the Department of Pathology, University of Chicago Medical Center, Chicago, Illinois. This article contains a summary of work supported in part by National Institutes of Health Grant 15062 and conducted at the Atherosclerosis Specialized Center of Research during the time at which both investigators were engaged in regression studies. It also reflects support now coming from National Institutes of Health Grant R10-HL33740, Bethesda, Maryland.

Address for reprints: Robert W. Wissler, PhD, MD, Department of Pathology, University of Chicago Medical Center, 5841 South Maryland, Box 414, Chicago, Illinois 60637.

Although several reports issued between 1927 and 1950 indicated that atherosclerosis or its clinical manifestations could be ameliorated after periods of severe nutritional deprivation, the majority of these studies were flawed.[1] Most of the studies had longitudinal designs, subjective and nonquantitative end points, and failure to differentiate beneficial changes in arterial plaques from changes in the blood that might decrease platelet and fibrin participation in thrombosis. Therefore, the decreases in ischemic brain strokes and heart attack rates may have been the result of regression of atherosclerosis or a decrease in the clinical effects of atherosclerosis.

Animal models of atherosclerosis began to attract attention in the first 2 decades of this century[2,3] with the pioneering investigations of the role of protein in atherogenesis in the rabbit, which, interestingly, turned into an investigation of the role of dietary cholesterol.

This model of atherosclerosis produced in the cholesterol-fed rabbit was often used in the next 50 or more years for investigations of the effects of intervention.[4] Unfortunately, these attempts were largely unsuccessful with regard to regression of preexisting lesions, probably due to the large stores of cholesterol that the rabbit builds up in its reticuloendothelial system. Subsequent reports indicated that if the ambient oxygen in the atmosphere is increased, rabbit lesions may be decreased or reversed.[5–7] Furthermore, increased ambient oxygen in combination with other agents that lower blood lipids (cholesterol) was found to produce highly significant regression of well-established and severe atherosclerotic lesions in rabbits.[8]

STUDIES IN NONHUMAN PRIMATES

This work, plus a remarkably positive paper reporting regression of advanced canine atherosclerosis by lipid-reducing (cholesterol-reducing) nutritional regimens,[9] set the stage for the first definitive regression study in nonhuman primates.

In several reports beginning in 1970, Armstrong et al[10] found that they could produce a very large increase in lumen diameter (size) of coronary arteries in severely atherosclerotic rhesus monkeys by a relatively simple, but sustained, shift of diets. They reported that when they changed the diets of these monkeys—from the high-fat, high-cholesterol diet they had used to produce the disease, to one low in fat and containing almost no cholesterol, with or without a substantial content of polyunsaturated fatty acids (corn oil)—the ≥60% stenosis of all the major coronary arteries was consistently reduced by al-

TABLE I Regression Studies In Rhesus Monkeys

Investigators (Year)	Induction Diet (Period in Months)	Lesion Severity	Regression Diet (Period in Months)	Regression Response
Armstrong et al (1970, 1972)	Egg yolk and cholesterol (17)	3+	Low fat or corn oil (40)	3+ improved
Tucker et al (1971, 1974)	Butter, beef, tallow and cholesterol (3)	1+	Chow (3-13)	1+ improved
Stary (1972, 1973)	Butter and cholesterol (3)	2+	Low-fat basal (1, 3, 10)	3+ improved
DePalma et al (1972)	Coconut oil, butter and cholesterol (14)	2+	Chow or chow and biliary diversion (9)	3+ improved
Vesselinovitch et al, (1973, 1975)	Coconut oil, butter and cholesterol (18)	3+	Low fat (corn oil) (18)	3+ improved
Kokatnur (1975)	Butter, beef, tallow and cholesterol (3)	1+	Chow (8 and 13)	1+ improved
Wagner et al (1975, 1976, 1980)	Lard and cholesterol (19)	3+	SC 300 mg/dl	1+ improved
			SC 200 mg/dl (24)	2+ improved
Chakravarti et al (1977)	Peanut oil and adrenaline HCl (5)	1+	Safflower oil (5)	3+ improved
			Low fat (5)	1+ improved
			Low fat, low calories (5)	2+ improved
Vesselinovitch and Wissler (1978, 1980, 1982)	Peanut oil and cholesterol (12)	3+	"Prudent" diet of corn oil and cholestyramine + atherogenic diet (12)	2+ improved
Weber et al 1977	Coconut oil and cholesterol (12)	3+	"Prudent" diet and cholestyramine (12)	2+ improved
DePalma et al (1980)	Egg yolk, sucrose, and cholesterol (24)	3+	Atherogenic diet and cholestyramine (21)	2+ improved
Mostofi and Goepp (1981)	Peanut oil and cholesterol (14)	3+	"Prudent" diet and cholestyramine (14)	2+ improved
Clarkson et al (1981)	Lard and cholesterol (19)	3+	SC 300 mg/dl (24, 48)	1+ improved
			SC 200 mg/dl (24, 48)	2+ improved
Wissler and Vesselinovitch (1983)	Coconut oil, butter and cholesterol (12)	3+	Atherogenic diet and cholestyramine and probucol (12)	2+ improved

SC = Diet adjusted to yield serum cholesterol at given constant level.
Adapted with permission from Wissler and Vesselinovitch.[20]

most two thirds, to a stenosis of <25%. They also reported biochemical data indicating that the greatest reduction in the lipid components of the lesions was in the cholesteryl esters[11] and that both collagen and elastin gradually decreased as the lesions became smaller.[12]

After this work, many additional studies (Table I) used the rhesus monkey that Taylor et al[13–16] had studied and reported on in 1962 and 1963. The impressive features of this model that have led to its widespread use for atherosclerosis research are the remarkable resemblance of its lesions to human plaques grossly, topographically, microscopically, morphometrically, and in terms of clinical complications.

The evidence of regression reported by Armstrong and co-workers[17–19] was especially well illustrated by their photomicrographs. These show that the lesion components were remarkably altered, with a marked decrease in the lipid-rich necrotic cores—the intracellular and extracellular lipids surrounding the atheroma, including the monocyte-derived macrophage foam cells.

In general, the many other regression studies using rhesus monkeys (Table I) have confirmed and extended these observations.[20] Furthermore, these studies demonstrated that, without exception, this remarkably humanoid animal model consistently shows improvement in atherosclerotic lesions regardless of the type of therapy, method of evaluating lesion improvement or stage of disease.

Thus far, the only variables we have found to have a definite influence on regression are the type of food fat used to produce the plaque,[21] the involvement of the artery wall in an inflammatory process,[22,23] and the degree of increase in cholesterol turnover used to induce regression.[24]

Our studies have concentrated on the combined use of cholesterol-reducing diets and lipid-reducing drugs. Our results, which have been published in many reports, have indicated that substantial regression can be documented, regardless of whether one measures these effects grossly,[25] by micropoint-counting methods,[26] by microcomputer-assisted digitizer morphometry,[27] or by biochemical and isotopic tracers.[24] The findings have also indicated that the total body cholesterol load is remarkably reduced using these therapeutic approaches. In some of the experiments, isotopic labels were used to study the lability of the collagen, elastin and cholesterol in the lesion.

We conducted 9 regression studies using the rhesus monkey model (Table II), and some in which responses in this model were compared with those in cynomolgus and stump tail monkeys. In several instances, different methods of induction and different methods of intervention were compared. Also, several of the studies were planned and conducted so that many of the biochemical and morphologic features could be measured quantitatively at 4-month intervals during the genesis and the treatment of the atherosclerotic lesions.

Figure 1 (a, b and c) presents the most common exper-

imental designs followed in these studies. Reference groups were evaluated at the beginnings of intervention and at the conclusions of the studies to facilitate comparisons of many features of the lesions before and after treatment. The use of reference groups made it possible to measure the effects of therapy on lesion size and lesion components.

In general, the results of all these studies indicate that animals treated with cholestyramine in addition to a very low fat, low-cholesterol ration show approximately 2 times more improvement in their aorta and coronary artery atherosclerosis (with regard to factors such as lesion size, lesion thickness, and loss of lipid from the plaques) compared with animals treated with the therapeutic dietary regimen alone (Fig. 1a).

Table III summarizes the results of the measurements of aortic lesion size, as recorded in 3 consecutive male rhesus monkey studies using a modification of the method of Howard.[28] In these 3 experiments, the conditions of induction and therapy were very similar (Fig. 1a). It is evident that the results of the gross morphometry were remarkably uniform and the following general statements can be made:

1. The lesions continue to develop progressively in the second 12 months of hypercholesterolemia (group II).

2. A low-fat, essentially cholesterol-free ration during the second 12 months of the study results in a marked reduction in lesion size of approximately one third (group III).

3. Cholestyramine, a bile-acid sequestrant, leads to a reduction in lesion size of one half to one third.

4. Combined therapy with cholestyramine and the low-fat, low-cholesterol diet results in lesions that cover only one sixth to one eighth of the intimal surface involved before therapy (reference group I).

Other convincing evidence of regression of atherosclerosis in the rhesus monkey has resulted from combined therapy with cholestyramine and probucol administered after 1 year of an atherogenic ration; the monkeys continued consuming the high-fat, high-cholesterol ration during therapy (Fig. 1b).[29]

A few of the results of the timed studies (Fig. 1c) are presented graphically in Figure 2.[20,30] These findings indicate that almost half the decrease in lesion area occurs during the first 4 months of a 12-month regression period using a low-fat, cholesterol-poor ration. Much of this decrease is probably due to the fact that two thirds of the microscopically stainable lipid is removed during this same 4-month period, even though this effect does not manifest as gross intimal lesion reduction or reduction in lesion thickness until later.

Additional studies have been completed in which the regression of atheromatous lesions that resulted from feeding the monkeys peanut oil were compared with those that resulted from feeding them a diet containing the same amount of cholesterol, but with a mixture of coconut oil and butter as the source of dietary fat. These results indicated that the peanut-oil-induced lesions regressed effectively, but more slowly than did the much more lipid-rich lesions produced by the high-cholesterol, coconut-oil-containing ration.[20]

TABLE II Regression Studies in Rhesus Monkeys at the University of Chicago, 1968–1982

Study Code	Year	Study Description
RH-18	1969–1971	First study in rhesus monkeys using drugs plus diet to demonstrate reversal of plaque
RH-27 RH-31 RH-32	1973–1975 1974–1976 1975–1977	Three similar studies using cholestyramine and a low-fat, low-cholesterol diet, evaluated quantitatively with gross-point counting and computer-assisted and digitized micromorphometry and biochemical methods to measure regression
CY-35 RH-37 RH-38 CY-39	1977–1979 1978–1980 1979–1981 1980-1982	Four studies of progression and regression in rhesus and cynomolgus monkeys in which the results were quantitatively evaluated at 4-month intervals
CY-39	1980–1982	Probucol and cholestyramine combined to treat rhesus monkeys with advanced atherosclerosis; the monkeys were fed a high-fat, high-cholesterol ration during therapy.

In these studies examining rhesus monkeys at various intervals during progression and regression of their atheromatous lesions, the other major comparisons were between the progression and regression of atherosclerotic disease in cynomolgus and rhesus macaques. The cynomolgus monkey showed much more extensive disease early and a retardation in the rate at which regression took place.

The results of our studies[22] and others[23] indicate that the cynomolgus lesions are very difficult to utilize in effective regression studies because, although the lesions are rich in lipid, they involve large areas of the media, and in this respect they are different from most plaques in human arteries, which are usually largely intimal. We have referred to this as atheroarteritis because these lesions typically involve all 3 layers of the artery and because they show abundant inflammatory cells in the intima, media and adventitia. In the case of the muscular arteries, the scarring of the damaged media in the cynomolgus monkey leads to constriction and narrowing of the lumen when the lipid is removed. Obviously, this is not a beneficial effect.

FACTORS AFFECTING REGRESSION AND PROGRESSION

As these studies have continued, it has become evident that at least some of the differences between rhesus and cynomolgus lesions are due to circulating immune complexes that our cynomolgus monkeys consistently demonstrate and that influence endothelial integrity.[31] These are characterized by a much more actively destructive and inflammatory process with many more monocyte-derived foam cells in the media. These observations indicate that immunologic phenomena may help accelerate and intensify atherogenesis and may lead to a concentric and often transmural process that is quite different in its histologic features as well as its potential for regression. In one experiment with rhesus monkeys, the percentage

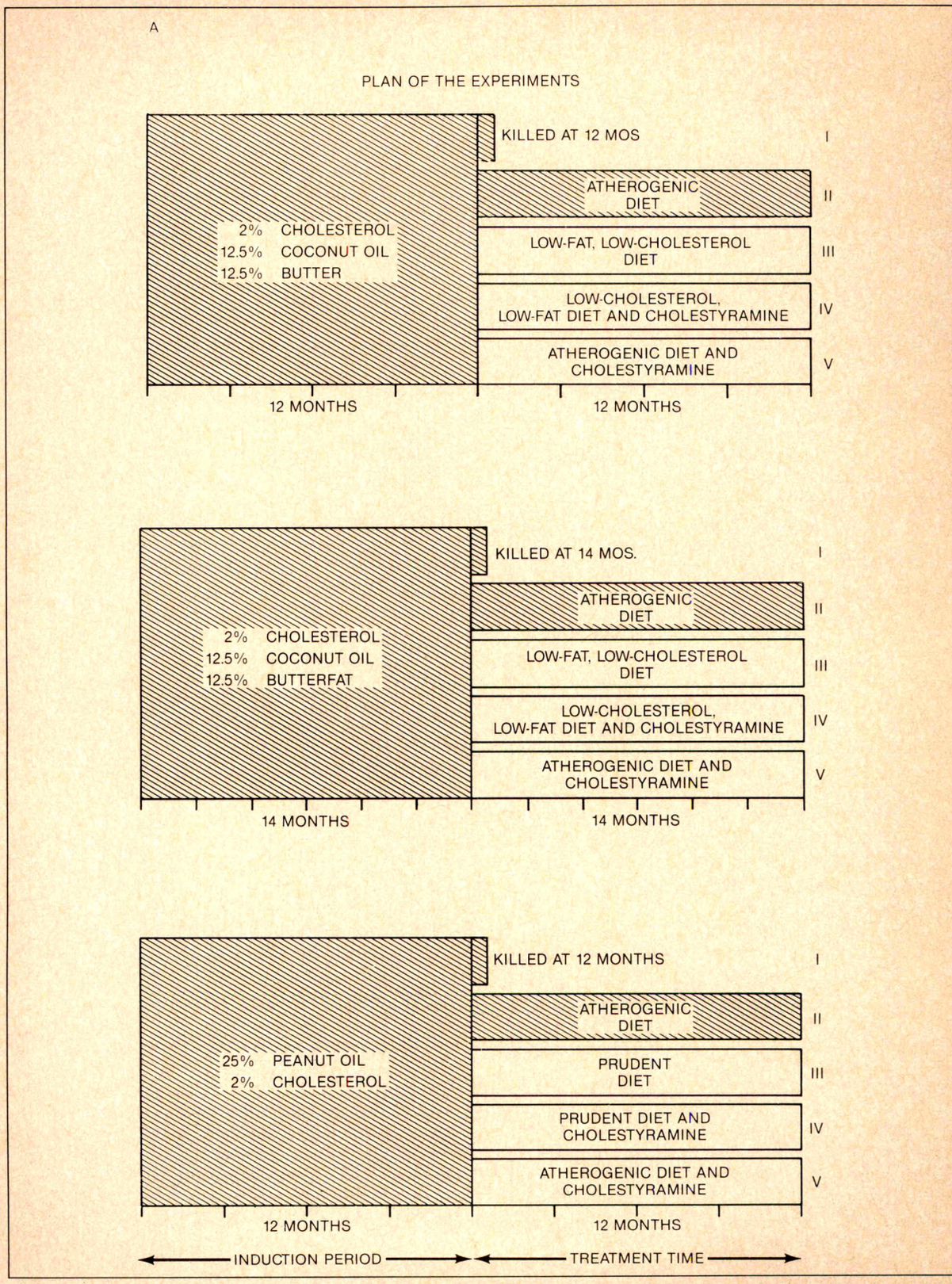
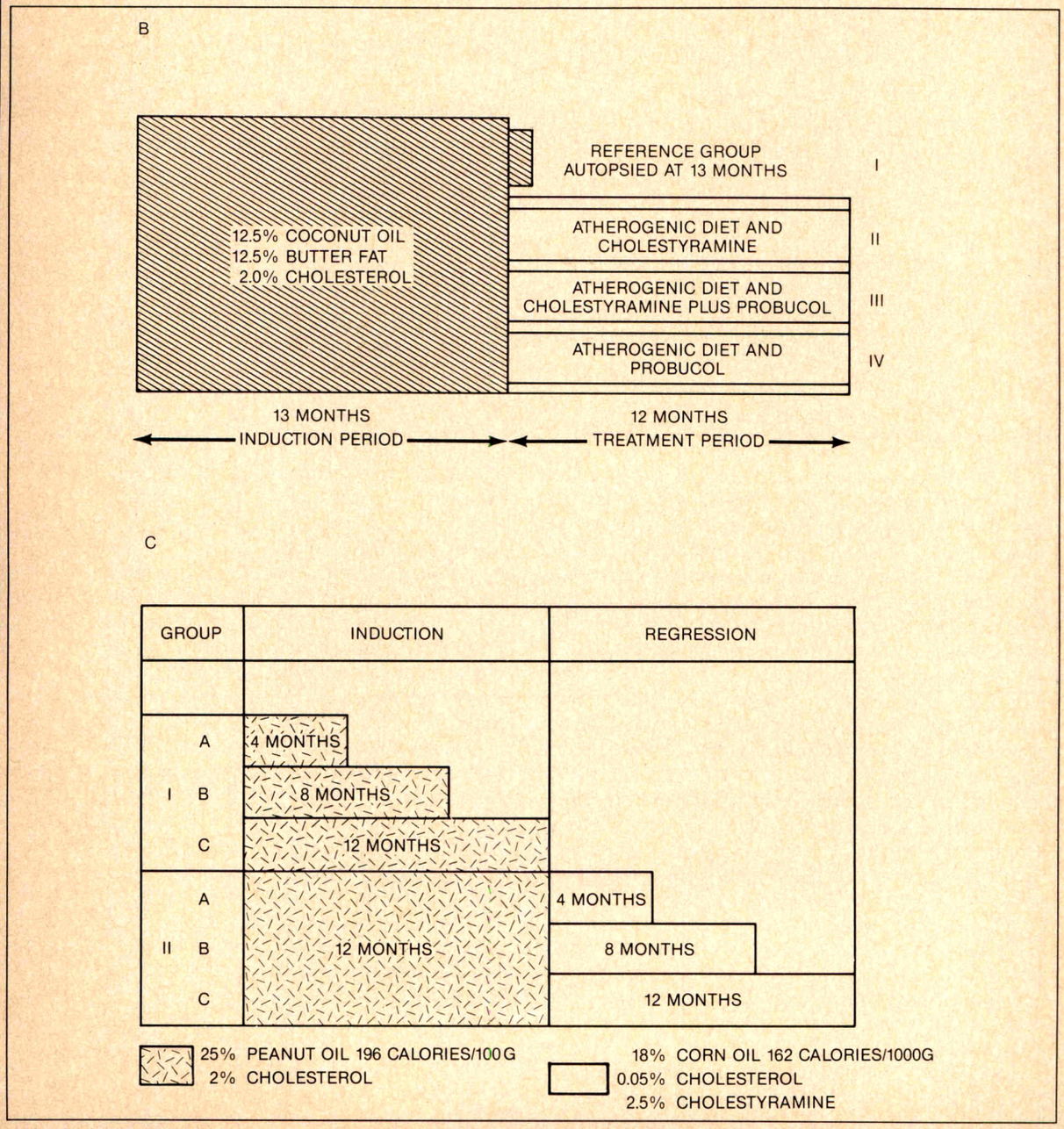


FIGURE 1. Three experimental plans used in the 9 University of Chicago Nonhuman Primate Regression studies, each approximately 24 months in length, completed between 1969 and 1982 (Table II). In general, these studies involved a 1-year period of induction of atheromatous lesions using highly atherogenic rations, followed by a 1-year period of treatment in more than 200 animals. Suitable reference groups of comparable animals were studied before and after intervention. In addition to quantitative

of aortic intima involved decreased from 82 to 13% in 12 months. In an identical study, the cynomolgus monkey failed to show any reduction in intimal disease during a similar period (i.e., 78 and 77% involved at the 2 time periods). The disease actually appeared to increase slightly after 4 months of therapy. Similar resistance to regression of atherosclerosis in the coronary arteries of this species has been reported by Hollander et al.[23]

Other factors are likely to influence regression of experimental atheromatous lesions. These factors are just beginning to be studied systematically as toxic reactions that may help sustain injury to the cells of the artery wall by means of oxidation and peroxidation of low-density lipoprotein and very low density lipoprotein along with free radical formation after these lower-density lipoproteins enter the artery wall.[32,33] This phenomenon, which appears to be suppressed by powerful antioxidants such as probucol,[34] may ultimately be of substantial importance in accelerating progression of atherosclerosis as well as explaining the importance of this type of toxicity in suppressing regression of atheromatous lesions.

Two other aspects of the atheromatous process are



evaluation of blood lipid values, gross and microscopic lesion sizes, and additional morphologic and biochemical lesion components, cholesterol and connective tissue turnover studies, total carcass cholesterol determinations, and many other determinations were included in selected studies.

TABLE III Gross Aortic Lesions in Three Regression Studies

Groups	Atherogenesis and Treatments	Gross Aortic Intimal Lesions (% of Total) RH-27 (12 + 12 mo)	RH-31 (14 + 14 mo)	RH-32 (12, 12 mo)	Average
I	Coconut oil 12.5% Butterfat 12.5% Cholesterol 2.0%	62 ± 14.2	68 ± 9.5		66 ±2.0
	Peanut oil 25.0% Cholesterol 2.0%			68 ± 3.9	
II	Coconut oil 12.5% Butterfat 12.5% Cholesterol 2.0%	84 ± 6.9	73 ± 4.8		82 ± 4.5
	Peanut oil 12.5% Cholesterol 2.0%			88 ± 4.3	
III	Low-fat, low-cholesterol diet	23 ± 9.9			23 ± 1.7
	Prudent diet: Corn oil 18.0% Cholesterol 0.05%		20 ± 8.4	26 ± 11.0	
IV	Low-fat, low-cholesterol diet plus cholestyramine (2.5%)	10 ± 5.6			10 ± 1.5
	Prudent diet plus cholestyramine (2.5%)		7 ± 2.5	12 ± 3.4	
V	Coconut oil/butterfat/cholesterol plus cholestyramine (2.5%)	31 ± 8.2	43 ± 12.0		32 ± 5.8
	Peanut oil/cholesterol plus cholestyramine (2.5%)			23 ± 12.1	

probably of major importance in influencing its continued progression. One is the increasing endothelial damage, which is evident as the plaques become larger. The second is the continuing excessive smooth-muscle-cell proliferation and matrix protein synthesis (collagen, elastin and proteoglycans) that we now associate with phenotypic modulation of the usually quiescent arterial smooth muscle cells as the atherogenic stimuli are sustained.

We now have strong indications that both of these pathologic reactions of the artery wall are rather promptly suppressed when the blood lipids are lowered by dietary or other means. Endothelial healing during regression has been documented by Weber and co-workers[35] in collaboration with Vesselinovitch in our regression studies using rhesus monkeys. That the decrease in cell proliferation is an important part of the process of plaque regression has been demonstrated very well by the studies in the swine model reported by Daoud et al[36] and Fritz et al.[37]

The details of plaque regression at the artery wall level are very difficult to study in human subjects. The various features of regression, as we now understand it from numerous animal studies (especially those in nonhuman primates and in swine), are shown in Figure 3. The major changes to be noted are the loss of lipid (both from the necrotic core as well as from the cellular parts of the plaque), the healing of the damaged endothelium, the remodeling and condensation of the fibrous elements, and the general decrease in cellularity that probably reflects the decreased mitotic activity of the arterial smooth muscle cells. All these changes probably contribute directly or indirectly to regression.

CONCLUSION

Although a limited amount of circumstantial evidence accumulated before 1970 suggested that the atherosclerotic plaque and the clinical effects of this pathologic process could be favorably influenced by decreasing fat, cholesterol and caloric intake, almost no reliable anatomic evidence for this phenomenon was available until very recently.

During the past 20 years, abundant evidence from experimental models of atherosclerosis has indicated that substantial regression of advanced plaques can be demonstrated after sustained reduction of the circulating lower-density blood lipoproteins by means of diet or cholesterol-lowering drugs, or both. This observation has given the biomedical scientific community the opportunity to study the details of regression and to learn more about the factors that may help augment or hinder this process. It has also opened up the opportunity to study the cell biological and chemical mechanisms by which regression occurs and to produce practical models of a regression regimen that can be applied to human subjects.

We are now entering the era in which relatively small clinical trials, with end points established by quantitative imaging of plaque size and plaque components measured with noninvasive techniques, can be expected to yield definitive results and help establish the validity and effec-

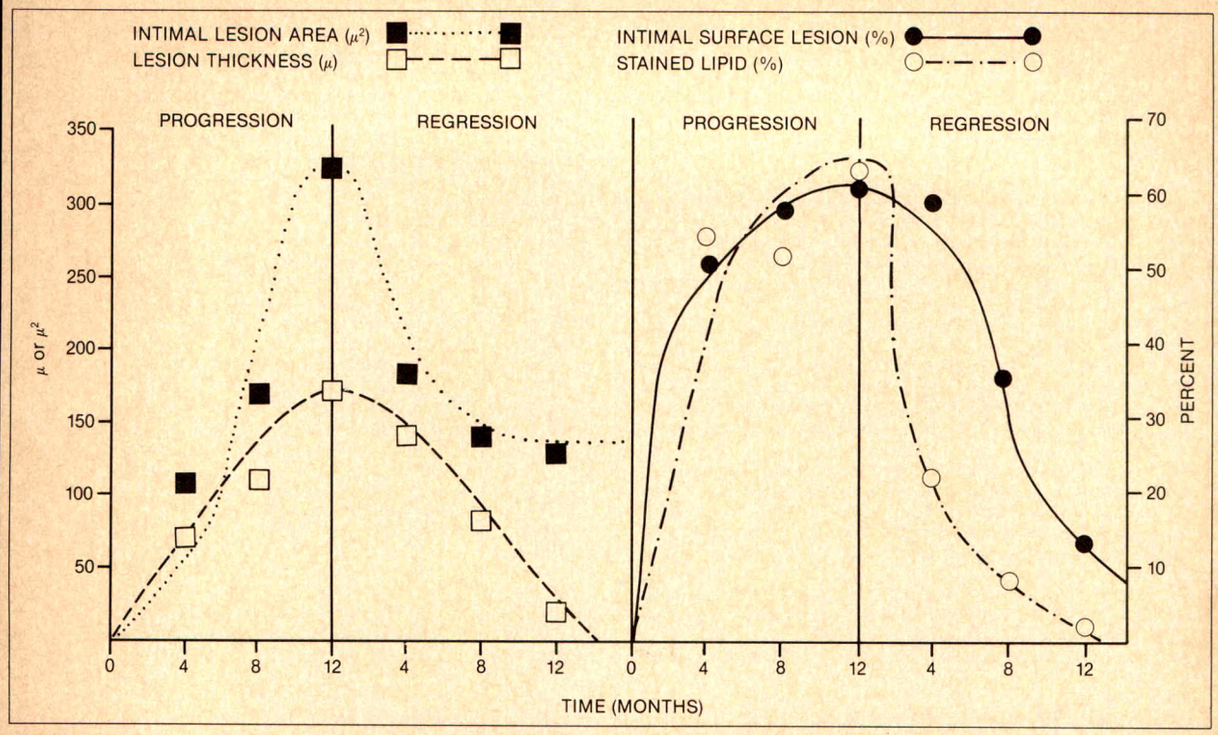


FIGURE 2. Rate of progression and regression of selected features of aortic atherosclerosis in rhesus monkeys with time. Features include intimal lesion area and maximal lesion thickness (*left*) and the percent of intimal surface covered with lesion grossly and percent intimal lesion area stained for lipid (*right*). (Reproduced with permission from Wissler and Vesselinovitch[20] and *Plenum Publishing Corp.*)

tiveness of various types of therapeutic approaches designed to reduce the size and clinical dangers of atherosclerotic plaques in several critical and vital locations (such as the carotid, coronary and iliac arteries). The Cholesterol Lowering Atherosclerosis Study, headed by Blankenhorn et al[38] at the University of Southern California, is one example of a successful study illustrating some of these approaches.

Acknowledgment: The data and illustrative material presented, as well as the preparation of this manuscript, have benefited greatly from the expert assistance of Gertrud Friedman and the word-processing skills of Alexander Arguelles and Megan Wai Mok.

REFERENCES

1. Wissler RW, Vesselinovitch D. Studies of regression of advanced atherosclerosis in experimental animals and man. *Ann NY Acad Sci 1976;275:363–378.*
2. Ignatowski A. Ueber die Wirkung des tierischen Eiweisses auf die Aorta und die parenchymatosen Organe der Kaninchen. *Virchows Arch Pathol Anat Physiol Klin Med 1909;198:248–270.*
3. Anitschkow N, Chalatow S. Uber experimentelle Cholesterinsteatose und ihre Bedeutung fur die Enstehung einiger pathologischer Prozesse. *Z Allg Pathol Anat*

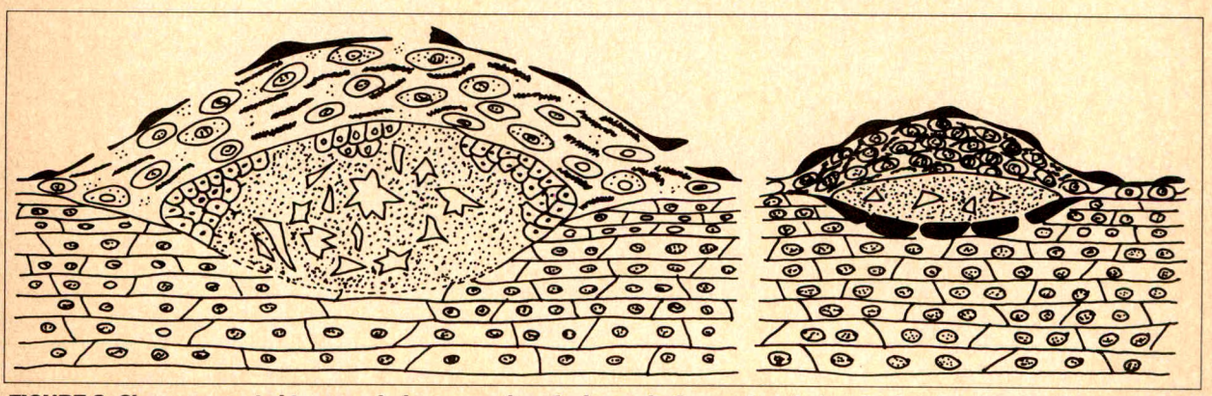


FIGURE 3. Changes reported to occur during regression of advanced atheromatous lesions in rhesus monkey and swine models. The plaques become substantially smaller, and both the fibrous cap and the components of the necrotic center decrease in size. Intracellular lipid virtually disappears, and extracellular lipid decreases. The collagen and elastin condense and remodel themselves to fit the smaller lesion, and the endothelial damage heals. (Reproduced with permission from Wissler RW and *WB Saunders.*)

1913;24:1–12.

4. Anitschkow, NN. A history of experimentation on arterial atherosclerosis in animals. In: Blumenthal HT, ed. Cowdry's Arteriosclerosis. 2nd ed. *Springfield, IL: Charles C. Thomas, 1977:405–413.*

5. Altschul R, Herman IH. Influence of oxygen inhalation on cholesterol metabolism. *Arch Biochem Biophys 1954;51:308–309.*

6. Altschul R. Einfluss von Sauerstofftherapie auf experimentelle Cholesterinatherosklerose. *Z Kreislauf Forsch 1955;44:129–132.*

7. Lisovsky VA, Mikushkin MK. The effects of oxygen on the development of experimental atherosclerosis in rabbits. *Pathol Physiol Exp Ther 1962;6:1–33.*

8. Vesselinovitch D, Wissler RW, Fischer-Dzoga K, Hughes R, DuBien L. Regression of atherosclerosis in rabbits. I. Treatment with low fat diet, hyperoxia, and hypolipidemic agents. *Atherosclerosis 1974;19:259–275.*

9. Bevans M, Davidson JD, Kendall FE. Regression of lesions in canine arteriosclerosis. *Arch Pathol 1951;51:288–292.*

10. Armstrong ML, Warner ED, Connor WE. Regression of coronary atheromatosis in rhesus monkeys. *Circ Res 1970;27:59–67.*

11. Armstrong ML, Megan MB. Lipid depletion in atheromatous coronary arteries in rhesus monkeys after regression diets. *Circ Res 1972;30:675–680.*

12. Armstrong ML. Connective tissue changes in regression. In: Schettler G, Goto Y, Hata Y, Klose G, eds. Atherosclerosis IV. *Berlin: Springer Verlag, 1977;405–413.*

13. Taylor CB, Cox GE, Manalo-Estrella P, Southworth J. Atherosclerosis in rhesus monkeys. II. Arterial lesions associated with hypercholesteremia induced by dietary fat and cholesterol. *Arch Pathol 1962;74:16–34.*

14. Taylor CB, Trueheart RD, Cox GE. Atherosclerosis in rhesus monkeys. III. The role of increased thickness of arterial walls in atherogenesis. *Arch Pathol 1963;76:14–28.*

15. Taylor CB, Manalo-Estrella P, Cox GE. Atherosclerosis in rhesus monkeys. V. Marked diet-induced hypercholesteremia with xanthomatosis and severe atherosclerosis. *Arch Pathol 1963;76:239–249.*

16. Taylor CB, Patton DE, Cox GE. Atherosclerosis in rhesus monkeys. VI. Fatal myocardial infarction in a monkey fed fat and cholesterol. *Arch Pathol 1963;76:404–412.*

17. Armstrong ML, Megan MB. Lipid depletion in atheromatous coronary arteries in rhesus monkeys after regression diets. *Circ Res 1972;30:675–680.*

18. Armstrong ML, Megan MB. Arterial fibrous proteins in cynomolgus monkeys after atherogenic and regression diets. *Circ Res 1975;36:256–261.*

19. Armstrong ML. Regression of atherosclerosis. In: Paoletti R, Gotto AM, eds. Atherosclerosis Reviews. Vol. 1. *New York: Raven Press, 1976:137–182.*

20. Wissler RW, Vesselinovitch D. Interaction of therapeutic diets and cholesterol-lowering drugs in regression studies in animals. In: Malinow MR, Blaton VH, eds. Regression of Atherosclerotic Lesions. *New York: Plenum, 1984:21–41.*

21. Vesselinovitch D, Wissler RW. Correlation of types of induced lesions with regression of coronary atherosclerosis in two species of macaques. In: Noseda G, Fragiacomo C, Fumagalli R, Paoletti R, eds. Lipoproteins and Coronary Atherosclerosis. *Amsterdam: Elsevier, 1982;401–406.*

22. Vesselinovitch D, Wissler RW. Reversal of atherosclerosis: comparison of non-human primate models. In: Gotto AM Jr, Smith LC, Allen B, eds. Atherosclerosis V (Proceedings of the 5th International Symposium). *New York: Springer Verlag, 1980:369–374.*

23. Hollander W, Kirkpatrick B, Paddock J. Colombo M, Nagraj S, Prusty S. Studies on the progresion and regression of coronary and peripheral atherosclerosis in the cynomolgus monkey. I. Effects of dipyridamole and aspirin. *Exp Mol Pathol 1979;30:55–73.*

24. Borensztajn J, Getz GS, Wissler RW. The in vitro incorporation of (^{3}H thymidine into DNA and of ^{32}P into phospholipids and RNA in the aorta of rhesu monkeys during early atherogenesis. *Atherosclerosis 1973;17:269–280.*

25. Howard CF Jr. Aortic atherosclerosis in normal and spontaneously diabeti Macaca nigra. *Atherosclerosis 1979;33:479–493.*

26. Vesselinovitch D, Wissler RW, Schaffner T. Quantitation of lesions during progression and regression of atherosclerosis in rhesus monkeys. In: Naito H, ed Nutrition and Heart Disease. *New York: SP Medical and Scientific Books 1982:121–149.*

27. Wissler RW, Vesselinovitch D, Schaffner TJ, Glagov S. Quantitating rhesu monkey atherosclerosis progression and regression with time. In: Gotto AM Jr Smith LC, Allen B, eds. Atherosclerosis V (Proceedings of the 5th Internationa Symposium). *New York: Springer Verlag, 1980:757–761.*

28. Howard CF Jr. Aortic atherosclerosis in normal and spontaneously diabeti *Macaca nigra. Atherosclerosis 1979;33:479–493.*

29. Wissler RW, Vesselinovitch D. Combined effects of cholestyramine and probucol on regression of atherlosclerosis in rhesus monkey aortas. *Appl Patho 1983;1:89–96.*

30. Wissler RW. Chairman's introduction to workshop on regression. In Schettler G, Gotto AM, Middelhoff G, Habenicht AS, Jurutka KR, eds. Atherosclerosis VI (Proceedings of the 6th International Symposium). *Berlin: Springer Verlag, 1983;183–186.*

31. Wissler RW, Vesselinovitch D, Davis HR, Lambert PH, Bekermeier M. A new way to look at atherosclerotic involvement of the artery wall and the functional effects. *Ann NY Acad Sci 1985;454:9–22.*

32. Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum JL. Beyond cholesterol: modifications of low-density lipoprotein that increase its atherogenicity. *N Engl J Med 1989;320:915–924.*

33. Jurgens G, Hoff HF, Chisolm GM III, Esterbauer H. Modification of human serum low density lipoprotein by oxidation—characterization and pathophysical implications. *Chem Phys Lipids 1987;45:315–336.*

34. Carew TE, Schwenke DC, Steinberg D. Antiatherogenic effect of probucol unrelated to its hypocholesterolemic effect: evidence that antioxidants in vivo can selectively inhibit low density lipoprotein degradation in macrophage-rich fatty streaks and slow the progression of atherosclerosis in the Watanabe heritable hyperlipidemic rabbit. *Proc Natl Acad Sci USA 1987;84:7725–7729.*

35. Weber G, Fabbrini P, Resi L, Jones R, Vesselinovitch D, Wissler RW. Regression of arteriosclerotic lesions in rhesus monkey aortas after regression diet: scanning and transmission electron microscope observations of the endothelium. *Atherosclerosis 1977;26:535–547.*

36. Daoud AS, Jarmolych J, Augustyn JM, Fritz KE, Singh JK, Lee KT. Regression of advanced atherosclerosis in swine. *Arch Pathol Lab Med 1976; 100:372–379.*

37. Fritz KE, Augustyn JM, Jarmolych J, Daoud AS, Lee KT. Regression of advanced atherosclerosis in swine. Chemical studies. *Arch Pathol Lab Med 1976;100:380–385.*

38. Blankenhorn DH, Nessim SA, Johnson RL, Sanmarco ME, Azen SP, Cashin-Hemphill L. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA 1987;257:3233–3240.*

39. Wissler RW. Principles of the pathogenesis of atherosclerosis. In: Braunwald E, ed. Heart Disease: A Textbook of Cardiovascular Medicine. 2nd ed. *Philadelphia: WB Saunders, 1984:1183–1204.*

Can Atherosclerotic Lesions Regress? Angiographic Evidence in Humans

David H. Blankenhorn, MD

Evidence that atherosclerotic lesions can regress is derived from autopsy findings in starved human populations, animal-model studies of induced atherosclerosis, and clinical trials using angiography. Three angiographic trials, with a total of 317 subjects, have demonstrated stabilization of lesions. One of these trials has revealed clear evidence of lesion regression.

(Am J Cardiol 1990;65:41F–43F)

From the Department of Medicine, Atherosclerosis Research Institute, University of Southern California School of Medicine, Los Angeles, California.

Address for reprints: David H. Blankenhorn, MD, Atherosclerosis Research Institute, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles, California 90033.

Information from several sources indicates that atherosclerosis can show regression. These sources include morphologic and biochemical studies of arterial lesions obtained at autopsy from starved human populations, animal experiments in which atherosclerosis is induced and then allowed to regress, and serial-imaging studies of arterial lesions in living human subjects. A variety of imaging procedures can potentially be used for evaluation of atherosclerosis, but angiography has been most widely performed and is the current preferred method for tracking coronary lesions. Early reports on angiographic change were principally based on retrospective evaluation of films obtained for routine clinical purposes; now, however, data from an impressive number of controlled angiographic clinical trials are available, and as many as 1,500 subjects are currently being studied.

The amount of information to be gained from angiography is subject to significant limitations; lesions can be imaged only at infrequent intervals, and the images show only intraluminal lesions. Nonetheless, we can now identify individual lesions that have changed, and current evidence clearly indicates that lesions can become smaller. Ultrasound and magnetic resonance imaging promise to augment the information derived by angiography because these newer methods probe the arterial wall in different ways and can be used at frequent intervals. Both ultrasound and magnetic resonance imaging have been used more effectively in peripheral and aortoiliac vessels than in the coronary arteries. To date, published serial observations on arterial lesion change have emanated from ultrasound studies of the carotid and proximal superficial femoral arteries.[1,2] The resolution of ultrasound imaging is low (relative to x-ray), and changes must be larger before they are detectable, but population-wide surveys using ultrasound are planned[3] and standardized grading procedures for serial evaluation of carotid lesions have been developed.[4]

ATTRIBUTES OF ATHEROSCLEROTIC LESION CHANGE

When lesion change has been carefully measured by serial angiography, the direction and magnitude of change present a continuous distribution. Almost all lesions in the center of the distribution exhibit no change. To one side of the central cluster of stable lesions are those that have progressed; on the opposite side are a lesser number that have regressed, but the curve has no apparent breaks to suggest that lesion change falls into discrete classes. Brown et al[5] published extensive measurements of coronary lesion change based on angiograms separated by an average of 13 months.

The continuous distribution of lesion change may be due to many small-scale events that vary in magnitude from lesion to lesion. This concept is in keeping with what is known of the cellular and metabolic processes involved in atheroma growth. Lesions are known to be composed principally of connective tissue produced by proliferation of dedifferentiated medial smooth muscle cells. Counts of individual lesions show widely differing numbers of viable cells; therefore, even though a strong single signal may trigger cellular activity in all lesions at one time, the resulting change in lesions is likely to vary from one lesion to the next.

Serial evaluation of human atherosclerosis has also shown that coronary lesions in the same person can change in opposite directions. This was one of the most interesting results of the National Heart, Lung, and Blood Institute Type II Intervention Trial,[6] in which 6 of 116 subjects treated with cholestyramine or placebo had progressing coronary lesions while other coronary lesions exhibited regression. Untreated lesions have a general tendency to progress. Regression therapy (which, although effective, does not strongly force change in the direction of improvement) might be expected to tip the balance partially and produce mixed lesion responses.

CURRENT EVIDENCE FROM SERIAL CORONARY ANGIOGRAMS IN 317 SUBJECTS

The National Heart, Lung, and Blood Institute Type II study was a randomized, placebo-controlled, double-blind trial that included both men and women.[6] This investigation tested the effects of 24 g of cholestyramine in subjects with type II hyperlipoproteinemia and overt coronary disease. At entry, total cholesterol levels averaged 323 mg/dl; triglycerides, 164 mg/dl; high-density lipoprotein cholesterol, 39 mg/dl; and low-density lipoprotein cholesterol, 251 mg/dl. The average baseline blood pressure was 122/79 mm Hg, and 43% of subjects smoked. A low-fat diet reduced low-density lipoprotein cholesterol levels by 5% in both groups. During the interval between angiograms, low-density lipoprotein cholesterol levels were reduced an additional 5% in the placebo group and 26% in the cholestyramine-treated group.

The original study design called for 250 patients randomized to 2 treatment arms, but recruitment was discontinued after 54 months, at which point 143 patients had been randomized. Angiograms were first recorded after 2 years in 31 subjects, but when apparent change was found in only 9, the schedule for repeat angiograms was lengthened to 5 years. Eventually, 116 subjects (57 randomized to placebo and 59 to cholestyramine) underwent repeat angiography, which was evaluated in pairs (with the baseline angiograms); the temporal sequence and treatment were masked. Results from 3 separate panels of 3 angiographers were combined for the final analysis. On average, the panelists evaluated 5.4 lesions per subject. The subjects were classified as showing definite progression, probable progression, definite regression, probable regression, mixed response, or no change.

Analysis of the findings revealed definite progression in 35% of the placebo group vs 25% of the drug-treated group, and probable progression in 14 vs 7%, respectively. No change was found in 42% of the placebo group vs 53% of the treated group. Probable regression was seen in 5% of the placebo group vs 3% of the drug-treated group, and definite regression was seen in 2 vs 3%, respectively. Mixed response (with lesions changing in opposite directions in the same subject) was found in 2% of the placebo group and in 8% of the treated group. Although the number of subjects evaluated did not allow definite conclusions, the investigators suggested that cholestyramine had retarded the progression of coronary atherosclerosis. An additional conclusion, drawn after baseline demographic inequalities and lesion severity were taken in account, was that a treatment effect could be demonstrated in a group of lesions with $\geq$50% stenosis, because 33% of such lesions in the placebo group vs 12% in the cholestyramine-treated group showed progression ($p < 0.05$).

The Leiden Intervention Trial, conducted from 1978 to 1981, presented evidence of an effect of diet on coronary atherosclerosis.[7] The subjects were 61 patients with stable angina and 1 or more lesions with >50% stenosis who were not candidates for coronary bypass surgery. The trial was not randomized or blinded; however, coronary angiograms were evaluated by readers who did not know either the blood lipid levels or order of the examinations. All patients were required to adhere to a vegetarian diet, which reduced the intake of saturated fat and cholesterol while increasing polyunsaturated fat. It was estimated that the diet at entry provided 11% of calories from saturated fat and 8.5% from unsaturated fat, and that daily cholesterol intake was 88 mg per 1,000 calories. After 1 year, diet estimates indicated 6.6% of calories from saturated fat and 16.8% from polyunsaturated fat, with a daily cholesterol intake of 30 mg per 1,000 calories. Among 53 subjects who started the diet, 4 died in the first year (3 with myocardial infarction and 1 suddenly), and 7 patients underwent coronary artery bypass grafting. Repeat angiography was not performed in 3 patients (because of a malignant tumor in 2 and refusal in 1). Repeat angiography was performed in 39 patients and the films were evaluated by both visual inspection and computer analysis.[7] Of the 39 patients, 21 showed progression and 18 no progression of atherosclerosis.

The Cholesterol Lowering Atherosclerosis Study was a selectively blinded, placebo-controlled trial with end points in native coronary arteries, aortocoronary venous bypass grafts, and femoral and carotid arteries.[8] The 188 subjects were randomized to either drug plus diet or placebo plus diet. All subjects were nonsmoking men aged 40 to 59 years who had previously undergone coronary artery bypass surgery. Total plasma cholesterol levels at entry ranged from 185 to 350 mg/dl. Combined colestipol plus niacin therapy produced a 26% reduction in total plasma cholesterol levels, 43% reduction in low-density lipoprotein cholesterol levels, and 22% reduction in plasma triglyceride levels, plus a simultaneous 37% elevation of high-density lipoprotein cholesterol levels. These lipid changes were achieved with aggressive use of drugs and intensive desktop–computer-assisted dietary counseling.[9]

At the time the study was truncated because of clear angiographic evidence of benefits from therapy, 162 subjects had completed 2 years of combined treatment with colestipol plus niacin. Coronary angiograms were reviewed by a panel of expert angiographers as a safety surveillance measure before assessment by computerized image processing.[10]

Treatment produced a significant reduction in the progression of atherosclerosis in native coronary arteries—both in the average number of lesions that progressed per subject ($p < 0.03$) and in the percentage of subjects with new atheroma formation ($p < 0.03$). The average number of native coronary lesions in drug-treated subjects was 10.9 per subject, and the average number of lesions showing increased stenosis was 1 per subject. The average number of native coronary lesions in placebo-treated subjects was 11.2 per subject, and the average number of lesions showing increased stenosis was 1.4 per subject. Among 80 drug-treated subjects, 8 (10%) developed new native coronary lesions, and 18 of 82 placebo-treated subjects (22%) developed new native coronary lesions.

Treatment also significantly reduced the percentage of subjects with any adverse change in bypass grafts ($p < 0.03$), as well as the percentage of subjects with new lesions ($p < 0.04$). The average number of grafts in both the drug-treated and placebo groups was 2.7. Among drug-treated subjects, 24% had an adverse change (increased stenosis or increased, diffuse edge irregularity) in 1 or more bypass grafts. In the placebo group, 39% of subjects showed adverse change in bypass grafts. New graft lesions developed in 14 of 80 subjects in the treated group (18%) vs 25 of 82 (30%) in the placebo group.

The deterioration observed in the overall status of the coronary arteries (as judged by the extent of obstructive lesions in native coronary arteries or abnormalities of bypass grafts, or both) was significantly less in the treated than in the placebo group ($p < 0.001$). In fact, atherosclerosis regression (as indicated by perceptible improvement in overall coronary status) was evident in 16.2% of the treated group vs 3.6% of the placebo group ($p = 0.002$).

CLINICAL IMPLICATIONS

The clinical implications of these results are that therapy after coronary bypass surgery should routinely include measures to reduce blood cholesterol levels. Follow-up of large numbers of patients who have undergone coronary artery bypass surgery indicates that, with current medical therapy, 44% of patients with venous bypass grafts will require a repeat operation in 10 years,[11] but patients whose lesions do not show progression have improved chances of survival and lower rates of myocardial infarction.[12]

REFERENCES

1. Hennerici M, Rautenberg W, Trockel U, Kladetzky RG. Spontaneous progression and regression of small carotid atheroma. *Lancet 1985;1:1415–1419.*

2. Poli A, Colombo A, Tremoli E, Pignoli P. Spontaneous progression of small carotid atheroma detected by echotomography (letter). *Lancet 1985;2:559–560.*

3. Lenzi S, Bucci A, Crepaldi G, Mancini M, Menotti A, Paoletti R, Spagnoli LG, Ventura A, Weber G. The CNR program of preventive medicine—SP4 Objective 44. Non-invasive techniques for the evaluation of atherosclerotic plaque progression or regression. *Mongr Atherosclerosis 1986;14:83–90.*

4. Crouse JR, Harpold GH, Kahl FR, Toole JF, McKinney WM. Evaluation of a scoring system for extracranial carotid atherosclerosis extent with B-mode ultrasound. *Stroke 1986;17:270–275.*

5. Brown BG, Bolson EL, Dodge HT. Arteriographic assessment of coronary atherosclerosis. Review of current methods, their limitations, and clinical implications. *Arteriosclerosis 1982;2:2–15.*

6. Brensike JF, Levy RI, Kelsey SF, Passamani ER, Richardson JM, Loh IK, Stone NJ, Aldrick RF, Battaglini JW, Moriarty DJ, Fisher MR, Friedman L, Friedewald W, Detre KM, Epstein SE. Effects of therapy with cholestyramine on progression of coronary arteriosclerosis: results of the NHLBI Type II Coronary Intervention Study. *Circulation 1984;69:313–324.*

7. Arntzenius AC, Kromhout D, Barth JD, Reiber JH, Bruschke AV, Buis B, van Gent CM, Kempen-Voogd N, Strikwerda S, van der Velde EA. Diet, lipoproteins, and the progression of coronary atherosclerosis. The Leiden Intervention Trial. *N Engl J Med 1985;312:805–811.*

8. Blankenhorn DH, Nessim SA, Johnson RL, Sanmarco ME, Azen SP, Cashin-Hemphill L. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA 1987;257:3233–3240.*

9. Johnson RL, Selzer R, Blankenhorn DH, Nessim S, Harlow C, Caldarara L, Azen SP. Nutrient Analysis System—a computerized seven-day food record system. *J Am Diet Assoc 1983;83:667–671.*

10. Blankenhorn DH, Johnson RL, Nessim SA, Azen SP, Sanmarco ME, Selzer RH. The Cholesterol Lowering Atherosclerosis Study (CLAS): design, methods, and baseline results. *Controlled Clin Trials 1987;8:354–387.*

11. Loop FD, Cosgrove DM. Repeat coronary bypass surgery: selection of cases, surgical risks, and long-term outlook. *Mod Concepts Cardiovasc Dis 1986;55:31–36.*

12. Moise A, Bourassa MG, Theroux P, Taeymans Y, Pasternac A, Campeau L, Bois MA, Dyrda I, David PR. Prognostic significance of progression of coronary artery disease. *Am J Cardiol 1985;55:941–946.*

13.12.

The American Journal of Cardiology

MAY 2, 1990

A Symposium: Indapamide and Antihypertensive Strategy

GUEST EDITORS:

Helios Pardell, MD, PhD
Professor of Medicine
Red Cross Hospital
Department of Internal Medicine
Hospitalet de Llobregat
Barcelona, Spain

Paul M. Vanhoutte, MD, PhD
Professor of Medicine and Pharmacology
Director, Center for Experimental Therapeutics
Baylor College of Medicine
Texas Medical Center
Houston, Texas, USA

CALCUTTA UNIVERSITY

A YORKE MEDICAL JOURNAL/CAHNERS PUBLISHING COMPANY

The American Journal of Cardiology

MAY 2, 1990 VOL. 65 NO. 17

A Symposium: Indapamide and Antihypertensive Strategy

GUEST EDITORS:

Helios Pardell, MD, PhD
Professor of Medicine
Red Cross Hospital
Department of Internal Medicine
Hospitalet de Llobregat
Barcelona, Spain

Paul M. Vanhoutte, MD, PhD
Professor of Medicine and Pharmacology
Director, Center for Experimental Therapeutics
Baylor College of Medicine
Texas Medical Center
Houston, Texas, USA

This symposium was held April 28, 1989, in Barcelona, Spain, under the auspices of the Spanish League Against Arterial Hypertension and was supported by the Institut de Recherches Internationales Servier.

EDITOR-IN-CHIEF
William C. Roberts, MD

MANAGING EDITOR, SPECIAL PROJECTS
Judith Wagner

PUBLISHER, SPECIAL PROJECTS
Kenton T. Finch

PRODUCTION EDITOR
Joan Gunning

PROOF EDITOR
Mary Crowell

THE AMERICAN JOURNAL OF CARDIOLOGY.® (ISSN 0002-9149) May 2, 1990, Vol. 65, No. 17 (USPS: 505–750).

Member, American Business Press, Inc. and Audit Bureau of Circulations. Published 4 times in January, February, March, May, June, July, September and October, 3 times in April, August and November, and 2 times in December, by The Cahners Publishing Company, a Division of Reed Publishing USA, 275 Washington St., Newton, MA 02158-1630. Terrence M. McDermott, President; Jerry D. Neth, Vice President/Publishing Operations; J.J. Walsh, Financial Vice President/Magazine Division; Thomas J. Dellamaria, Vice President/Production and Manufacturing.
SUBSCRIPTIONS: Solicited only from cardiologists and other physicians. Publisher reserves the right to refuse unqualified subscribers. Subscribers agree that no article or any part thereof published in any editions of the American Journal of Cardiology received under this subscription agreement may be copied, recorded or reproduced in any form or by any means, electronic or mechanical, including, among other things, photocopying or the storing of part or all of such articles on any information retrieval system, without the written permission of the Publisher. Address correspondence regarding subscriptions and changes of address to: THE AMERICAN JOURNAL OF CARDIOLOGY, 44 Cook Street, Denver, Colorado 80206-5800 (1-800-637-6073). Please include your zip code and, in case of change of address, copy of old address label. Changes of address must reach the Journal one month preceding month of issue. Single copy price: Regular issues $10.00; Symposium and special issues $12.00. Subscription rate for individuals in field of publication: United States 1 year $66, 2 years $112, 3 years $158; Canada and all other countries 1 year $105, 2 years $178, 3 years $252; Residents and Medical Students: United States 1 year $33; Canada & all other countries 1 year $85. Institutions: United States 1 year $95, 2 years $162, 3 years $228; Canada & all other countries 1 year $125, 2 years $213, 3 years $300. Air Mail available at additional charge of $150 per year. The Journal is not responsible for replacing missing issues unless the Circulation Department is notified of nonreceipt within 3 months of issue date.
Second class postage paid at Denver, CO, and at additional mailing office. Printed in U.S.A. Trademark™ in U.S. Patent Office. © Copyright 1990 by Reed Publishing USA: Saul Goldweitz, Chairman; Ronald G. Segel, President and Chief Executive Officer. All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording or by any information storage retrieval system, without permission of the copyright owner. Prices on bulk reprints of articles available on request.
The Publisher assumes no liability for any material published in the Journal. All statements are the responsibility of the authors.
MANUSCRIPTS: Address all manuscripts to William C. Roberts, MD, Editor-in-Chief, the American Journal of Cardiology, 7960 Old Georgetown Road, Suite 2C, Bethesda, Maryland 20814.

POSTMASTER: Send address changes to: The American Journal of Cardiology, 44 Cook Street, Denver, Colorado 80206-5800.

Cahners Publishing Company, A Division of Reed Publishing USA □ Specialized Business Magazines for Building & Construction □ Manufacturing □ Foodservice & Lodging □ Electronics & Computers □ Interior Design □ Printing □ Publishing □ Industrial Research & Technology □ Health Care □ Entertainment.

Publisher's Note

The opinions expressed in this presentation are those of the panelists and are not attributable to the sponsor or the publisher, editor, or editorial board of The American Journal of Cardiology. Clinical judgment must guide each physician in weighing the benefits of treatment against the risk of toxicity. References made in the articles may indicate uses of drugs at dosages, for periods of time, and in combinations not included in the current prescribing information.

Editor's suggestion: The symposium issues for a full year should be bound together separately from the regular issues.

CONTENTS

The American Journal of Cardiology

MAY 2, 1990 VOL. 65 NO. 17

A SYMPOSIUM: INDAPAMIDE AND ANTIHYPERTENSIVE STRATEGY

1H
Introduction
Helios Pardell and Paul M. Vanhoutte

2H
Antihypertensive Strategy: A Current and Prospective Review
Helios Pardell

6H
Effects of Indapamide on Endothelium-Dependent Relaxations in Isolated Canine Femoral Arteries
Valérie B. Schini, John Dewey, and Paul M. Vanhoutte

11H
Cardiovascular Protective Properties of Indapamide
D. Bruce Campbell and François Brackman

28H
Effects of Indapamide on the Mechanical Properties of the Arterial Wall in Deoxycorticosterone Acetate-Salt Hypertensive Rats
Bernard I. Levy, Pierre Poitevin, and Michael Safar

33H
Cardiovascular Effects of Antihypertensive Drugs — Involvement in the Therapeutic Choice
Manuel Luque-Otero and Carmen Fernandez-Pinilla

37H
Effects of Indapamide on Left Ventricular Mass and Function in Systemic Hypertension with Left Ventricular Hypertrophy
Michel Komajda, Krystoff Klimczak, Bernard Boutin, François Brackman, David Guez, and Yves Grosgogeat

43H
Role of Metabolic Risk Factors in Cardiovascular Prognosis of Systemic Hypertension
William J. Louis, Laurence G. Howes, Nora Straznicki, Henry Krum, Paddy Phillips, Jillian Broadbear, and John J. McNeil

46H
Efficacy of Antihypertensive Treatment with Indapamide in Patients with Noninsulin-Dependent Diabetes and Persistent Microalbuminuria
Sergio Gambardella, Simona Frontoni, Maria Grazia Felici, Vincenza Spallone, Patrizia Gargiulo, Susanna Morano, and Guido Menzinger

51H
Long-Term Diuretic Therapy and Renal Function in Essential Arterial Hypertension
Jose M. Alcazar, Jose L. Rodicio, and Luis M. Ruilope

55H
Diuretics and Transmembrane Ionic Exchanges: Structure-Activity Relations and Clinical Applications
Javier Diez

58H
Twenty-Four-Hour Blood Pressure Monitoring and Effects of Indapamide
Joan Ocon and Jose Mora

62H
Clinical Efficacy and Quality of Life with Indapamide Alone or in Combination with Beta Blockers or Angiotensin-Converting Enzyme Inhibitors
Dimitrios I. Athanassiadis, Constantinos G. Dimopoulos, Alexandros K. Tsakiris, Dionyssios F. Cokkinos, Achileas A. Tourkantonis, Pavlos K. Toutouzas, Bernard Boutin, and David Guez

67H
Long-Term Effects of Indapamide: Final Results of a Two-Year Italian Multicenter Study in Systemic Hypertension
Gastone Leonetti, Alessandro Rappelli, Antonio Salvetti, and Luigi Scapellato

72H
Diuretics and the Treatment of Systemic Hypertension
Pedro Aranda and Eduardo Lopez de Novales

77H
Beneficial Effects of Indapamide on Lipoproteins and Apoproteins in Ambulatory Hypertensive Patients
Isabelle Aubert, Francis Djian, and Jacques Rouffy

The American Journal of Cardiology

Introduction

Helios Pardell, MD, PhD, and Paul M. Vanhoutte, MD, PhD

The aim of antihypertensive treatment is no longer just to reduce blood pressure. One of the main interests of the meeting entitled "Antihypertensive Strategy for the 90's: From Pathology to Patient Well-Being" held in Barcelona in April 1989 was to review the wide choice of the major antihypertensive drugs available and to point out their individual characteristics, which impact on the quality of life.

The results of the studies performed over the last 10 years have demonstrated that modern antihypertensive treatment must fulfill 3 requirements: (1) lower blood pressure significantly, covering the whole nyctohemeral period, including early morning increase; (2) restore local blood flow with a necessary double impact: cardiac, by reducing left ventricular hypertrophy, and vascular, by improving arterial compliance; and (3) reduce long-term cardiovascular morbidity and mortality by treating hypertensive patients early, improving associated risk factors and administering drugs without any atheromatous side effects.

In addition to those requirements, antihypertensive agents must also permit compliance to the treatment and therefore low dosages are particularly important. Before administering an antihypertensive drug, its effects on other vital functions, especially renal function also must be taken into account. In this context, studies performed on indapamide, which has now been used for many years, have brought a new light to its unique mode of action.

Indapamide appears to have several intriguing effects on the vascular wall. It does not directly affect endothelium-dependent and independent relaxations; however, when prostanoid production is impaired, the compound facilitates the release of endothelium-derived relaxing factors and the direct action on vascular smooth muscle of prostanoids released from the endothelium. In addition, new pharmacologic data on indapamide demonstrate that it exhibits free-radical scavenging activity, which could protect the vascular smooth muscle.

In vivo, indapamide increases the arterial compliance in both normotensive- and hypertensive-treated rats. In humans, the efficacy of the drug at the dose of 2.5 mg once daily has now been confirmed using 24-hour blood pressure monitoring.

Indapamide has been used as monotherapy or in combination with an angiotensin-converting enzyme inhibitor or with a β blocker. In hypertensives who did not respond to a single agent, the combination of indapamide induced a decrease both in systolic and diastolic blood pressure values, with little or no adverse effects. Furthermore, questionnaires on quality of life showed a significant improvement in general well-being. Along these lines the final results of a 2-year multicenter study on hypertensive patients of the long-term effects of indapamide show that blood pressure is significantly reduced, with low metabolic effects. A mild reduction in serum potassium is observed, with a lower decrease than the one observed with thiazides, and without change in total cholesterol, high-density lipoprotein cholesterol and triglycerides. The compilation of 26 earlier studies permits the conclusion that indapamide is unique among diuretics because of either an absence of adverse lipid effects or even an improvement in high-density lipoprotein cholesterol.

It is well known that left ventricular hypertrophy is one of the most important risk factors in hypertension, leading to increased cardiovascular morbidity. Therefore, it has been of prime importance to evaluate the action of indapamide in cardiac hypertrophy. The results of a study performed in 1988 on 18 hypertensive patients taking indapamide over a 6-month period demonstrated a significant reduction of 16% in left ventricular mass index.

Diabetic nephropathy is a serious cause of morbidity and mortality in diabetes mellitus, and when the process is present, it cannot be reversed. Increasing attempts have been made to detect diabetic nephropathy at an earlier stage, leading to the concept of microalbuminuria. Indapamide given to 20 type II diabetic patients caused a constant and significant reduction in the albumin excretion rate and in the urinary IgG4 (recently proposed as a new marker of diabetic nephropathy) in the microalbuminuric group. Therefore, indapamide, a potent antihypertensive with low natriuretic action and specific vascular effect, presents many of the properties required for optimal cardiovascular protection.

This symposium will provide the readers of *The American Journal of Cardiology* with an in-depth discussion of new trends in hypertension, and the opportunity to familiarize themselves with indapamide, an intriguing member of the diuretic family. The guest editors would like to thank the Servier International Research Institute for making this meeting and the publication of its proceedings possible.

Antihypertensive Strategy: A Current and Prospective Review

Helios Pardell, MD, PhD

The efficacy of antihypertensive therapy in reducing cardiovascular complications has been clearly demonstrated in the last 20 years. Antihypertensives are particularly useful in the reduction of cerebrovascular complications which decrease by 60% on average in clinical trials on the treatment of mild and severe hypertension.

After the first clinical trials, the 1978 World Health Organization Experts Committee recommended the classic stepped-care (SC) approach with diuretics and β blockers as first-step agents. Other antihypertensive drugs, such as reserpine, centrally acting agents and vasodilators could be used in the next steps if blood pressure control was not achieved.

Both diuretics and β blockers have been widely used and the SC regimen has contributed to the better control of arterial hypertension in the community. The SC regimen has given general practitioners easy guidelines with which to treat hypertensive patients.

There are many reasons for modifying the classic SC approach. Prescription of antihypertensive drugs at high doses should be avoided and the use of new agents, such as calcium antagonists and angiotensin-converting enzyme inhibitors, is recommended. Demographic trends have brought about an increase in the aged population and, consequently, an increase in the proportion of elderly hypertensives. These patients present particular problems in long-term management, among which are a high frequency of other associated diseases and an important number of adverse effects caused by the classic antihypertensive drugs.

Nevertheless, diuretics are still useful in the treatment of hypertension, either as a monotherapy regimen or in association with other drugs. New diuretics, such as indapamide, have a very interesting pharmacologic profile with considerably fewer metabolic side effects on plasma cholesterol and glucose levels.

(Am J Cardiol 1990;65:2H–5H)

From the Department of Internal Medicine, Red Cross Hospital, Hospitalet de Llobregat, Barcelona, Spain.

Address for reprints: Helios Pardell MD, PhD, Department of Internal Medicine, Red Cross Hospital, 08906 Hospitalet de Llobregat, Barcelona, Spain.

The first follow-up studies of untreated hypertensive patients clearly showed that their survival rate did not exceed 5 years on average. Deaths were mostly a result of cardiac (coronary artery disease, cardiac failure), cerebrovascular (stroke) and renal (renal failure) complications.[1]

With the introduction of effective antihypertensive drugs, the mortality rate of treated hypertensive patients was greatly decreased, and their life expectancy increased considerably. Hamilton et al[2] and Wolff and Lindeman,[3] among others, reported very good results using ganglion-blocking agents, reserpine, diuretics and guanethidine in the treatment of severe hypertension.

The first Veterans Administration Study[4] showed a 56% reduction in all-cause mortality (100% in hypertensive fatal complications and 40% in atherosclerotic fatal complications) using reserpine and diuretics in the treatment schedule of severe hypertensives. The second study[5] also demonstrated the benefits of this therapeutic regimen in mild hypertensives (diastolic blood pressure 90 to 104 mm Hg); however, these investigators pointed out that the benefit of pharmacologic treatment was considerably lower in patients with diastolic blood pressure levels approximately 100 mm Hg than in patients with moderate or severe hypertension (Fig. 1).

The main objective of the Hypertension, Detection and Follow-up Program (HDFP)[6] was to evaluate the benefits of the stepped-care (SC) approach in the treatment of arterial hypertension. The SC group was treated with diuretics as a first-step agent with the successive addition of reserpine, hydralazine or guanethidine. The referrred-care (RC) group was treated with the drugs often prescribed by doctors in the United States at that time. After a 5-year follow-up, the all-cause and cardiovascular mortality in the SC group was, respectively, 17 and 19% lower than in the RC group. Similar findings were encountered in stratum 1 of the study, which consisted of hypertensives with diastolic blood pressure levels of 90 to 104 mm Hg (constituting about 70% of all participants in the study).

1978 stepped-care approach: In accordance with the studies mentioned, the USA Joint National Committee recommended in 1977 an SC regimen that included thiazides, reserpine and hydralazine in addition to the nonpharmacologic measures that constituted a first-line approach.[7]

One year later, in 1978, the Experts Committee of the World Health Organization proposed the more classic SC regimen with diuretics (widely prescribed in the USA) and β blockers (more frequently prescribed in Europe) as the first step and with the other antihypertensive

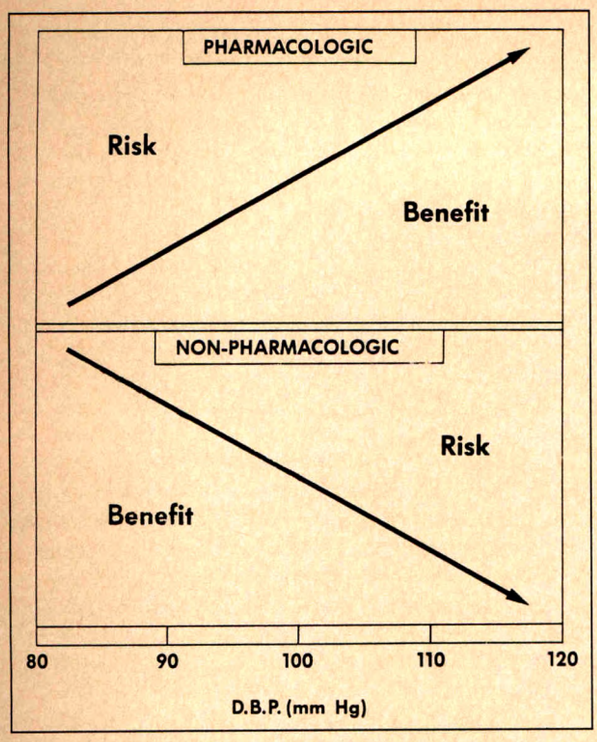


FIGURE 1. Risk/benefit of pharmacologic and nonpharmacologic antihypertensive treatment, according to diastolic blood pressure (D.B.P.) levels.

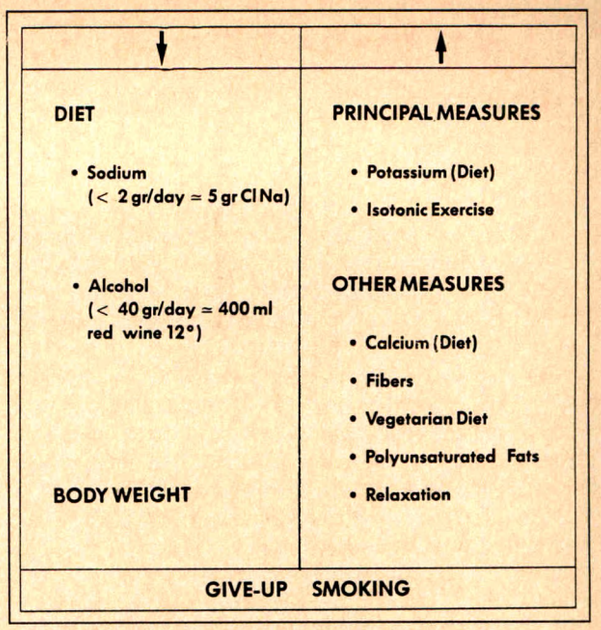


FIGURE 2. Nonpharmacologic treatment of hypertension.

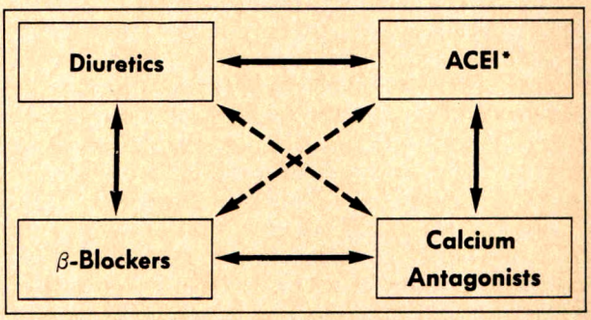


FIGURE 3. Possibilities for combining the first-step antihypertensive agents. *Solid line*, very useful; *broken line*, relatively useful. ACEI = angiotensin-converting enzyme inhibitors.

agents as successive steps in the event that the diuretics and β blockers did not control blood pressure when used at their highest therapeutic doses.[8]

The SC regimen had great success worldwide because it contributed to improving the antihypertensive treatment for a great number of patients. The most important virtue of SC treatment was to provide doctors with very easy guidelines and to introduce the idea that antihypertensive agents had different and gradual potencies. Moreover, it encouraged the use of diuretics and β blockers as a first-line approach, and this combination was capable of resolving antihypertensive problems in most cases. Virtually all clinical trials on the treatment of mild hypertension conducted in the 1980s involved the use of diuretics and β blockers and showed the unquestionable benefit of these drugs, which reduce cerebrovascular mortality among treated hypertensives by 60% on average and coronary mortality by 10%.[9,10] Extensive experience in the treatment of hypertension with diuretics and β blockers has allowed greater discernment in the choice of therapy used for various patient groups: β blockers for young hypertensives and patients with coronary artery disease; and diuretics for the elderly, black hypertensives and patients with cardiac failure.

Diuretic dilemma: Conflicting findings from clinical trials on the treatment of mild hypertension,[11] demographic trends toward an older population, and the introduction of new antihypertensive drugs have led to a questioning of the appropriateness of the SC approach.

One of the fundamental questions is the role of the diuretic in the light of reports that diuretics may produce negative cardiovascular effects as a result of their actions on serum potassium and cholesterol levels. We know that long-term diuretic therapy can produce a decrease in serum potassium of 0.5 to 0.7 mmol/liter.[12] Some studies[13,14] suggest that this could explain the increase in coronary mortality and sudden death in hypertensive patients treated with diuretics and in those who have baseline electrocardiographic abnormalities. Other investigators[15–17] refused this suggestion because of the following arguments: (1) Important and potentially dangerous decreases in serum potassium levels are observed only when diuretics are prescribed at high doses (100 mg/day of chlorthalidone or equivalent), but not when they are prescribed at lower doses (25 mg/day or equivalent). (2) The decrease in serum potassium in a patient is not accompanied by significant disturbances in the cellular content of the cation. (3) There is not enough experimental evidence on the effect of hypokalemia on the myocardium. (4) Studies, such as the HDFP,[6] principally included hypertensives treated with diuretics that did not interfere with a clear reduction in mortality rates. (5) The last study from

the Glasgow Hypertension Unit[16] showed no influence of hypokalemia on the mortality of hypertensive patients treated with diuretics. (6) Some investigators[17,18] pointed out that there is no clear evidence of coronary risk from diuretic-induced hypercholesterolemia, and that this increase is observed only in the acute period of treatment and not in long-term diuretic therapy.

Some researchers[19] suggested abandoning diuretics as a first-step antihypertensive agent. However, many others [18,20] are of the opinion that diuretics still have a place in the treatment of hypertension and recommend their use.

Diuretics are, in fact, widely used; physicians in the USA[21] prescribed them in 76% of cases as initial therapy of hypertension, and Spanish doctors[22] do so in 75% of patients on a monotherapy schedule, and in 27.5% of patients taking an associated drug.

The benefit of the SC approach is reemphasized in the Post Surveillance Study findings.[23] This study is based on 2 contacts with all participants in the HDFP Study[18] subsequent to the 6 to 7 years follow-up and was initiated with 2 principal objectives: (1) the collection of data regarding the mortality beyond the 5-year follow-up; and (2) the assessment of the post-trial treatment status and blood pressure control in SC and RC groups. At the end of the Post Surveillance Study, they reported:

A decrease in the number of SC and an increase in the number of RC hypertensive patients (this increase outweighs the change in the SC group unlike in the HDFP Study); a decrease of 8.9% in the level of blood pressure control (diastolic blood pressure <90 mm Hg) in the SC group. At the 5-year follow-up in the HDFP Study the SC group had 17.7% more hypertensives under control than the RC group, whereas at the end of the Post Surveillance Study this difference was only 5.9%.

An increase in the mean diastolic blood pressure of the SC group with a decrease in the difference between the SC and RC groups (4.9 mm Hg at the 5-year HDFP follow-up and only 1.7 mm Hg at the end of the Post Surveillance Study).

An increase in the SC group mortality rate with a corresponding decrease in the difference in the mortality of this group compared with the RC group (mortality was 18.7% lower in the SC group at the 6- to 7-year HDFP follow-up and merely 9% at the end of the Post Surveillance Study).

Treatment of hypertension for the 1990s: In general, the SC approach is still recommended in the treatment of hypertension, although it must be adapted to the changing therapeutic conditions: It is not advisable to prescribe antihypertensive agents at their maximal doses (in case of diuretics it is well demonstrated that lower doses maintain the antihypertensive efficacy with a significant reduction in adverse effects). It is preferable to substitute or add other drugs that can potentiate this effect; the new antihypertensive agents, such as calcium antagonists and angiotensin-converting enzyme (ACE) inhibitors, must be featured in the first-step approach. This allows an individualized schedule according to personal characteristics and, particularly, the cardiovascular risk profile of each hypertensive patient.

The last report of the Joint National Committee[24] pointed out that nonpharmacologic measures are still fundamental in any antihypertensive treatment, because they can control some mild hypertensives and can contribute substantially in cases in which treatment is essential (Fig. 2).

The recommendation regarding pharmacologic treatment is the use alone or in combination of any of the first-step agents: diuretics, β blockers, calcium antagonists, ACE inhibitors, and probably α blockers. The vasodilators and centrally acting agents should be reserved for the next steps in the event that blood pressure control is not achieved.

The classic (diuretics and β blockers) and recent antihypertensive drugs (calcium antagonists and ACE inhibitors) can be used in a variety of combinations with the view of reducing the doses used and, by the same token, the adverse effects. Regarding this point, diuretics are particularly interesting because their pharmacologic actions can amplify the antihypertensive effect of β blockers and ACE inhibitors, which act more efficaciously when plasma renin activity is high (Fig. 3).

In conclusion, diuretics may be used either in antihypertensive monotherapy regimens or in combination with other agents. Recent diuretic drugs, such as indapamide, give new possibilities because of their direct vascular effect and their influence on serum cholesterol levels and glucose metabolism.[25]

REFERENCES

1. Pickering GW. High Blood Pressure. 2nd ed. *London:Churchill Livingstone, 1968.*

2. Hamilton M, Thompson EN, Winiewski TKM. The role of blood pressure control in preventing complications. *Lancet 1964;1:235–238.*

3. Wolff FW, Lindeman RD. Effects of treatment in hypertension. Results of a controlled study. *J Chron Dis 1966;19:237–240.*

4. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. *JAMA 1967;202:1025–1034.*

5. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressures averaging 90 through 114 mm Hg. *JAMA 1970;213:1143–1152.*

6. Hypertension, Detection and Follow-up Program Cooperative Group. Five-year findings on the Hypertension, Detection and Follow-up Program. I. Reduction in mortality of persons with high blood pressure, including mild hypertension. *JAMA 1979;242:2562–2571.*

7. Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. *JAMA 1977;237:255–261.*

8. Report of W. H. O. Expert Committee; Arterial Hypertension. Tech. Rep. Series No. 628. *Geneva: WHO, 1978.*

9. Cutler JA, Furberg CD. Drug treatment trials in hypertension. A review. *Prev Med 1985;14:499–518.*

10. Pardell H. Hypertension therapy. Current and future strategies. *J Int Med Res 1988;6:suppl 1:2A–7A.*

11. Toth PJ, Horwitz RI. Conflicting clinical trials and the uncertainty of treating mild hypertension. *Am J Med 1983;75:482–488.*

12. Morgan DB, Davidson C. Hypokalemia and diuretics. An analysis of publications. *Br Med J 1980;280:905–908.*

13. Multiple Risk Factor Intervention Trial Research Group. Multiple Risk Factor Intervention Trial: risk factors and changes in mortality results. *JAMA 1982;248:1465–1477.*

14. Holme I, Helgeland A, Hjermann I, Leren P, Lund-Larsen PG. Treatment of mild hypertension with diuretics. The importance of ECG abnormalities in the

Oslo Study and MRFIT. *JAMA 1984;251:1296–1299.*
15. Papademetriou V. Diuretics, hypokalemia and cardiac arrhythmias: A critical analysis. *Am Heart J 1986;11:1217–1224.*
16. Robertson JWK, Isles CG, Brown I, Cameron HL, Coley H, Lever AJ, Murray GD. Mild hypokalemia is not a risk factor in treated hypertensives. *J Hypertens 1986;4:603–608.*
17. Moser M. Diuretics in the treatment of hypertension. *Med Clin North Am 1987;71:985–998.*
18. Moser M. In defense of traditional antihypertensive therapy. *Hypertension 1988;12:324–326.*
19. Zanchetti A. Re-examination of stepped care: a retrospective and prospective. *J Cardiovasc Pharmacol 1985;7:suppl:S126–S131.*
20. Freis ED. Choice of initial treatment. *J Cardiovasc Pharmacol 1985; 7:suppl:S112–S116.*
21. Gallup G Jr, Cotugno HE. Preference and practices of Americans and their physicians in antihypertensive therapy. *Am J Med 1986;81:suppl 6C:20–24.*
22. Pardell H, Tresserras R. The Spanish doctor and arterial hypertension. *Madrid: Spanish League against Arterial Hypertension, 1988.*
23. Hypertension, Detection and Follow-up Program Cooperative Group. Persistence of reduction in blood pressure and mortality of participants in Hypertension, Detection and Follow-up Program. *JAMA 1988;259:2113–2122.*
24. 1988 Joint National Committee. The 1988 Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. *Arch Intern Med 1988;148:1023–1038.*
25. Thomas JR. A review of 10 years of experience with indapamide as an antihypertensive agent. *Hypertension 1985;7:suppl II:152–156.*

Effects of Indapamide on Endothelium-Dependent Relaxations in Isolated Canine Femoral Arteries

Valérie B. Schini, PhD, John Dewey, PhD, and Paul M. Vanhoutte, MD, PhD

Indapamide is an effective antihypertensive agent in humans and in experimental hypertensive animals. The aim of the present study was to investigate whether indapamide affects endothelium-dependent and independent relaxations in canine femoral arteries. Rings (with or without endothelium) were contracted with prostaglandin $F_{2\alpha}$ (2×10^{-6} mol/liter) before the addition, in a cumulative fashion, of relaxing agents. Indapamide (10^{-7} to 10^{-4} mol/liter) had no direct effect on unstimulated or prostaglandin-stimulated preparations; it did not alter relaxations of preparations with endothelium induced by acetylcholine, bradykinin, adenosine diphosphate or the calcium ionophore A23187. Similarly, it did not affect relaxations induced by sodium nitroprusside, prostacyclin or forskolin in preparations with or without endothelium. Indomethacin shifted the concentration-response curve to bradykinin to the right and did not alter that to the other relaxing drugs. The reduced relaxation to bradykinin was reversed in a concentration-dependent manner by indapamide (10^{-7} to 10^{-5} mol/liter). In the presence of indomethacin, indapamide shifted the concentration response curve to prostacyclin (in rings with endothelium) and to forskolin (in rings with and without endothelium) to the left. Thus, indapamide does not directly affect endothelium-dependent and independent relaxations. However, when prostanoid production is impaired, indapamide facilitates the release of endothelium-derived relaxing factor(s), and to a lesser extent, the direct action on vascular smooth muscle of prostanoids (prostacyclin) released from the endothelium.

(Am J Cardiol 1990;65:6H–10H)

From the Center for Experimental Therapeutics, Baylor College of Medicine, Houston, Texas.

Address for reprints: Paul M. Vanhoutte, MD, Center for Experimental Therapeutics, Baylor College of Medicine, One Baylor Plaza, Room 826E, Houston, Texas 77030.

Indapamide [chloro-4-N-(methyl-2-indolinyl-1)-sulfamoyl-3-benzamide] is an orally active sulfonamide diuretic agent which reduces blood pressure in part by decreasing vascular reactivity and peripheral resistance.[1] Indapamide reduces vasoconstrictor responses in several isolated vascular preparations from rats and rabbits.[2–7] The inhibitory effects of indapamide have been attributed to a reduced entry of extracellular calcium through an effect on the plasma membrane, although the drug may also depress contractions evoked by the release of the activator ion from intracellular stores.[8–11]

The endothelium plays an obligatory role in the relaxation of isolated arteries caused by a number of vasodilator substances because it releases endothelium-derived relaxing factor(s).[12,13] The release of endothelium-derived relaxing factor(s) may contribute to the decrease in peripheral resistance previously observed with certain antihypertensive agents.[14] The present experiments were designed to determine whether the presence of the endothelium affects the action of indapamide on isolated arteries.

METHODS

Mongrel dogs (weighing 15 to 30 kg) of either gender were anesthetized with sodium pentobarbital (30 mg/kg intravenously). The femoral arteries were removed and placed in modified Krebs-Ringer bicarbonate solution of the following composition (mmol/liter): sodium chloride (NaCl) 118.3, potassium chloride (KCl) 4.7, calcium chloride ($CaCl_2$) 2.5, magnesium sulfate ($MgSO_4$) 1.2, potassium phosphate monobasic (KH_2PO_4) 1.2, sodium bicarbonate ($NaHCO_3$) 25.0, calcium disodium edetate 0.026, glucose 11.1 (control solution).

Organ chamber experiments: The blood vessels were cleaned of connective tissue and cut into rings (5 mm long). Special care was taken not to damage the luminal surface. In certain arteries, the endothelium was removed by gentle rubbing of the luminal surface with a cotton tip; the removal was confirmed by demonstrating the absence of relaxations to acetylcholine.[15,16] The rings were mounted horizontally between 2 stirrups in organ chambers filled with 25 ml of control solution aerated with 95% oxygen-5% carbon dioxide (37°C, pH 7.4). One stirrup was anchored, the other connected to a strain gauge (Gould UTC2) to determine changes in isometric force.

The rings were stretched in a stepwise fashion to the optimal point of their length-tension curve as determined by the tension developed to exposure at each level of stretch to KCl (20 mmol/liter; optimal tension approximately 10 g). The tissues then were allowed to equilibrate for 45 minutes.

TABLE I Effects of Indapamide and Indomethacin on Contractions Evoked by Prostaglandin $F_{2\alpha}$ (2×10^{-6} mol/liter) in Canine Femoral Artery*

Endothelium	No. of Dogs	Indapamide (mol/liter) Control	10^{-7}	10^{-6}	10^{-5}	10^{-4}
Without Indomethacin						
With	7	12.9 ± 2.6	12.2 ± 1.9	13.6 ± 2.1	11.8 ± 2.2	ND
Without	6	15.3 ± 3.1	ND	ND	ND	14.5 ± 2.6
With indomethacin (10^{-5} mol/liter)						
With	6	13.7 ± 1.7	12.3 ± 1.4	15.5 ± 3.4	15.2 ± 3.0	ND
Without	6	14.3 ± 2.7	ND	ND	ND	12.1 ± 2.9

* Data shown as mean ± standard error of the mean and expressed as absolute increases in tension (g). Indapamide did not have statistically significant effects.
ND = not determined.

All experiments were performed in parallel using rings with, and without, endothelium from the same blood vessels. Relaxations were examined in rings contracted with prostaglandin $F_{2\alpha}$ (2×10^{-6} mol/liter). In certain experiments, the rings were incubated with indomethacin (10^{-5} mol/liter for 45 minutes) to prevent the synthesis of endogenous prostanoids. Indomethacin did not affect contractions to prostaglandin $F_{2\alpha}$.

Drugs: The following drugs were used: acetylcholine chloride (Sigma Chemical Co., St Louis, Missouri); the calcium ionophore A23187 (Sigma); adenosine diphosphate (ADP) (Sigma); bradykinin (Sigma); forskolin (Sigma); indapamide (Laboratoires Servier, France); indomethacin (Sigma); prostacyclin (Sigma); and prostaglandin $F_{2\alpha}$ (Sigma). Indomethacin was dissolved in 10 ml of distilled water containing sodium carbonate (Na_2CO_3) (5×10^{-3} mol/liter) and was sonicated before use. Prostacyclin was dissolved with $NaHCO_3$ (0.15 mol/liter, pH = 9), and indapamide in pure ethanol; the rings not exposed to indapamide received the corresponding amount of ethanol (which did not significantly affect vascular responsiveness) (data not shown). All other drugs were prepared daily in distilled water and kept on ice until used. The concentrations are reported as the final molar concentration in the organ chamber.

Calculations and statistical analysis: The results are expressed as mean ± standard error of the mean. Unless otherwise specified, n is the number of animals from which rings were taken. Responses are expressed in rings contracted with prostaglandin $F_{2\alpha}$, as percent changes from the contracted levels. IC_{50} is the concentration of the tested agent that induces a 50% relaxation. Statistical evaluation of the data was performed using Student *t* test for paired or unpaired observations. Values were considered to be statistically different at $p < 0.05$.

RESULTS

Direct effects: Indapamide (10^{-7} to 10^{-4} mol/liter) did not significantly affect basal tension in rings of femoral arteries with and without endothelium in the absence or presence of indomethacin (10^{-5} mol/liter) (data not shown). Indapamide did not significantly affect contrac-

TABLE II Indapamide and Endothelium-dependent Relaxations in Canine Femoral Artery*

	Endothelium	No. of Dogs	Control E max	Control −log IC_{50}	Indomethacin† E max	Indomethacin† −log IC_{50}	Indapamide‡ E max	Indapamide‡ −log IC_{50}	Indomethacin† Plus Indapamide‡ E max	Indomethacin† Plus Indapamide‡ −log IC_{50}
Acetylcholine	(+)	7	100	7.97 ± 0.08	100	8.05 ± 0.07	100	7.62 ± 0.16	100	7.97 ± 0.23
Bradykinin	(+)	6	100	8.18 ± 0.10	93.3 ± 5.1	7.72 ± 0.07¶	100	8.25 ± 0.16	96.0 ± 4.0	8.15 ± 0.12§
ADP	(+)	6	90.7 ± 4.0	5.92 ± 0.15	84.9 ± 9.4	5.96 ± 0.14	90.7 ± 5.0	5.99 ± 0.16	92.6 ± 7.4	6.08 ± 0.20
A23187	(+)	7	99.6 ± 0.4	7.51 ± 0.07	100	7.60 ± 0.04	100	7.54 ± 0.09	100	7.58 ± 0.09
PGI_2	(+)	6	88.0 ± 5.1	6.68 ± 0.13	85.2 ± 8.2	6.65 ± 0.18	95.9 ± 3.1	6.79 ± 0.09	89.0 ± 5.8	6.89 ± 0.16§
	(−)	6	90.5 ± 5.7	6.78 ± 0.19	98.6 ± 1.0	6.84 ± 0.13	96.3 ± 3.7	6.93 ± 0.12	94.2 ± 2.7	6.95 ± 0.17
Forskolin	(+)	6	94.9 ± 2.1	6.70 ± 0.08	91.1 ± 5.2	6.63 ± 0.12	99.6 ± 0.4	6.83 ± 0.10	99.0 ± 1.0	6.87 ± 0.10§
	(−)	6	88.2 ± 5.7	6.66 ± 0.14	83.2 ± 6.5	6.52 ± 0.13	98.3 ± 1.2	6.81 ± 0.12	98.8 ± 0.8	6.77 ± 0.11§
Sodium nitroprusside	(−)	8	99.7 ± 0.3	7.96 ± 0.09	100	7.80 ± 0.09	100	7.87 ± 0.12	100	7.89 ± 0.09

* Data shown are mean ± standard error of the mean.
† (10^{-5} M).
‡ Indapamide was used at concentration of 10^{-5} M in the case of acetylcholine, bradykinin, ADP and A23187, and 10^{-4} M in the case of forskolin and PGI_2 and sodium nitroprusside.
§ Denotes a significant difference from the response observed in the presence of indapamide.
¶ Denotes a significant difference from control.
ADP = adenosine diphosphate; E_{max} = maximal relaxation of contractions induced by prostaglandin PGF_2 (2×10^{-6} M) caused by 10^{-5} M of ADP or 10^{-6} M of either acetylcholine, bradykinin, A23187, PGI_2, and forskolin; PGI_2 = prostacyclin; (+) = with endothelium; (−) = without endothelium.

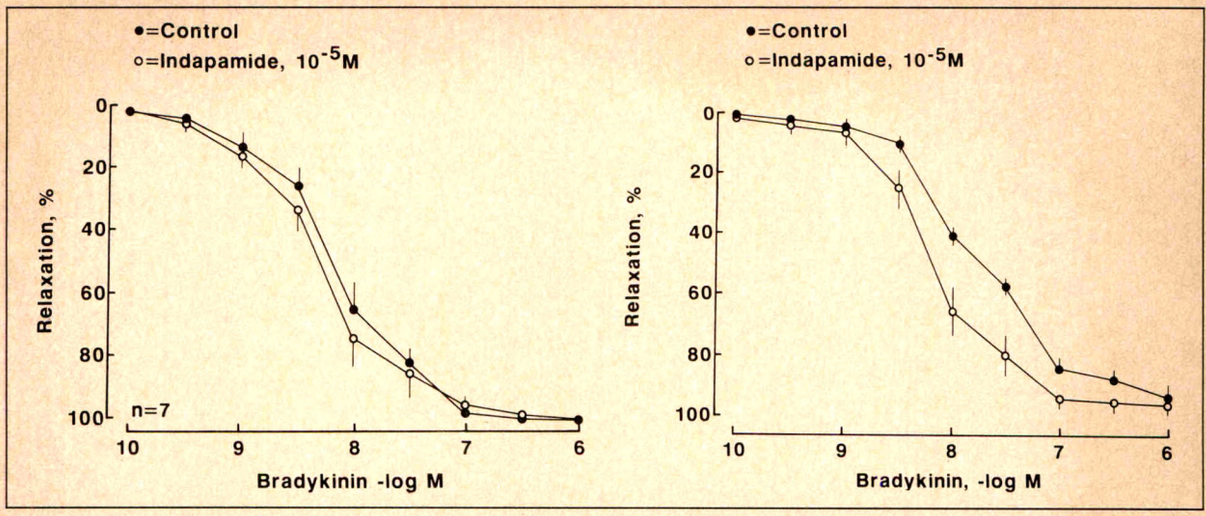


FIGURE 1. Relaxations to bradykinin in canine femoral arteries with endothelium contracted with prostaglandin $F_{2\alpha}$ (2×10^{-6} mol/liter), in the absence (*closed circles*) and presence (*open circles*) of indapamide (10^{-5} mol/liter). The experiments were performed in control solution (*left*) and after incubation with indomethacin (10^{-5} mol/liter) (*right*). Data shown are mean ± standard error of the mean. The relaxations are expressed as a percentage of the contraction to prostaglandin $F_{2\alpha}$.

tions evoked by prostaglandin $F_{2\alpha}$ (2×10^{-6} mol/liter), in the absence or presence of indomethacin (10^{-5} mol/liter; Table I).

Effect on relaxations: *Rings with endothelium:* In control solution, indapamide (10^{-7} to 10^{-4} mol/liter) did not significantly affect the relaxations evoked by acetylcholine (Table II), ADP (Table II), bradykinin (Fig. 1, left; Table II) or the calcium ionophore A23187 (Table II); these relaxations were endothelium-dependent (data not shown). Indomethacin (10^{-5} mol/liter) did not significantly affect the relaxations evoked by acetylcholine, ADP or A23187, but caused a significant shift to the right of the concentration-relaxation curve to bradykinin (Table II). In the presence of indomethacin, indapamide caused a concentration-dependent shift to the left of the concentration-response curve to bradykinin (Fig. 1, right; Table II), without affecting the responses to either acetylcholine (Table II), ADP (Table II) or the calcium ionophore (Fig. 2; Table II).

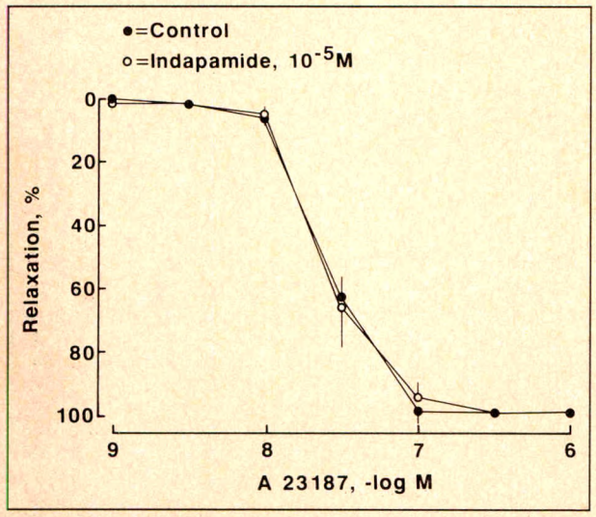


FIGURE 2. Relaxations to the calcium ionophore A23187 in canine femoral arteries with endothelium contracted with prostaglandin $F_{2\alpha}$ (2×10^{-6} mol/liter), in the absence (*closed circles*) and presence (*open circles*) of indapamide (10^{-5} mol/liter). The experiments were performed in the presence of indomethacin (10^{-5} mol/liter). Data shown are mean ± standard error of the mean.

In the rings contracted with prostaglandin $F_{2\alpha}$ in the presence of indomethacin (10^{-5} mol/liter), indapamide (10^{-4} mol/liter) caused a significant shift to the left of the concentration-response curve of prostacyclin and forskolin (Table II).

Rings without endothelium: All experiments were performed in rings without endothelium, incubated with indomethacin (10^{-5} mol/liter). They were contracted with prostaglandin $F_{2\alpha}$ (2×10^{-6} mol/liter) and exposed to increasing concentrations of either prostacyclin, forskolin or sodium nitroprusside. Indapamide (10^{-4} mol/liter) caused a significant shift to the left of the concentration-relaxation curve of forskolin, but not that of either prostacyclin or sodium nitroprusside (Fig. 3; Table II).

DISCUSSION

The present experiments demonstrate that indapamide does not induce the release of endothelium-derived relaxing factor(s). This conclusion is based on the observations that the compound did not evoke endothelium-dependent relaxations when the femoral arteries were contracted with prostaglandin $F_{2\alpha}$.[12,13] Likewise, it is unlikely that indapamide nonselectively facilitates the releases of endothelium-derived relaxing factor(s) by other vasoactive substances, because it did not potentiate the endothelium-dependent relaxations evoked by acetylcholine, ADP, and the calcium ionophore. In addition, because indapamide did not increase relaxations evoked in the absence of endothelium by sodium nitroprusside (which relaxes vascular smooth muscle by activating soluble guanylate cyclase as does endothelium-derived relaxing factor[s]),[17–19] it appears unlikely that indapamide

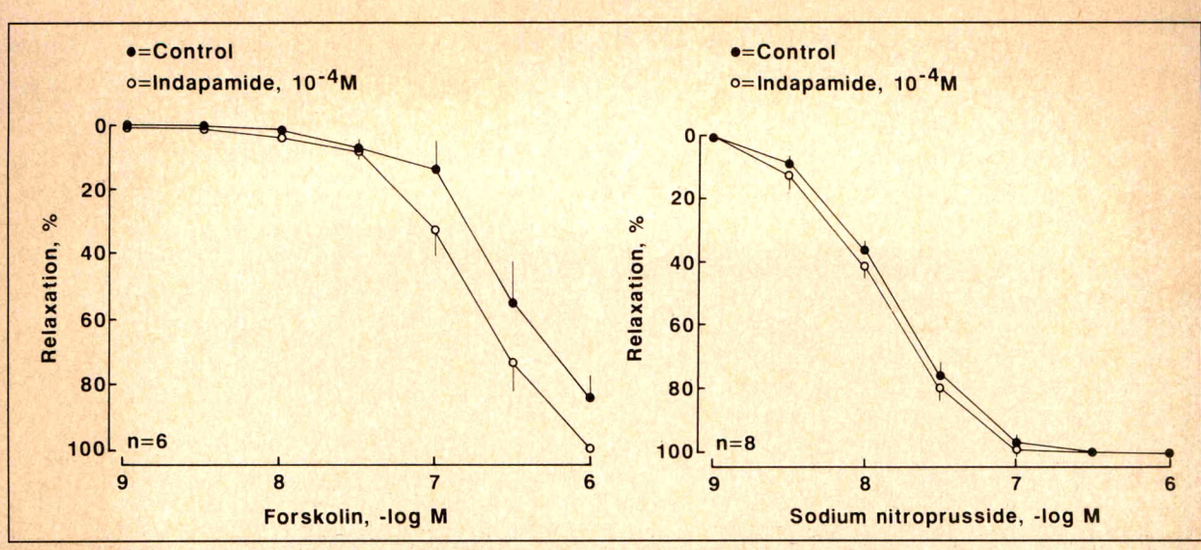


FIGURE 3. Relaxations to forskolin (*left*) and sodium nitroprusside (*right*) in canine femoral arteries (without endothelium, in the presence of 10^{-5} mol/liter indomethacin), contracted with prostaglandin $F_{2\alpha}$ (2×10^{-6} mol/liter). The experiments were performed in the absence (*closed circles*) and presence (*open circles*) of indapamide (10^{-4} mol/liter). Data shown are mean ± standard error of the mean.

affects the responsiveness of vascular muscle to activators of guanylate cyclase. Thus, the drug does not affect directly either the release or the effect of endothelium-derived relaxing factor(s), as may be the case for other antihypertensive agents such as β blockers[20,21] or converting enzyme inhibitors.[22]

Indapamide did not cause relaxations of canine femoral arteries without endothelium. A similar absence of direct inhibitory effect of the drug on vascular smooth muscle has been reported in another large conduit artery, the aorta of the rat.[23] The present observations are not necessarily in conflict with earlier reports in smaller arteries and in spontaneously active portal-mesenteric veins.[2–7,11] If the major direct inhibitor effect of indapamide on vascular smooth muscle is to prevent calcium entry,[8–11] earlier work in the canine femoral artery would predict a lack of inhibitory effect of the drug, to judge from the limited relaxations caused by diltiazem in that type of preparation.[24]

The inhibitor of cyclooxygenase, indomethacin, caused a rightward shift of the concentration-relaxation response curve to bradykinin without significantly affecting any other tested responses of the preparations. These observations imply that an interaction exists between metabolites of arachidonic acid and the endothelium-dependent response to the peptide. Bradykinin can cause the release of prostaglandins, particularly prostacyclin, from endothelial cells.[25,26] The inhibitory effect of indomethacin on the relaxations to bradykinin is surprising because the contrary would be expected. There are several examples in canine blood vessels of the release of contracting factors that can be prevented by inhibitors of cyclooxygenase.[27,28] Inhibitors of cyclooxygenase increase rather than depress endothelium-dependent relaxations.[29] Thus, the effect of indomethacin would be better explained if a release of cyclooxygenase product by the endothelium were to exert a positive feedback on the release of endothelium-derived relaxing factor(s) evoked by bradykinin. If this interpretation is correct, prostacyclin is the likely mediator, because, from evidence of work in porcine arteries, prostacyclin increases the release of endothelium-derived relaxing factor(s).[30]

The major finding of the present study was that, after incubation with indomethacin, indapamide potentiated the relaxations induced by bradykinin. This was observed only in the presence of indomethacin with bradykinin, but not with other endothelium-dependent dilators. Thus, a direct interference with the release or the action of endothelium-derived relaxing factor(s) cannot explain the phenomenon. Indapamide has been reported to increase the release of prostaglandins, particularly prostacyclin.[31,32] Thus, the present data would be explained if

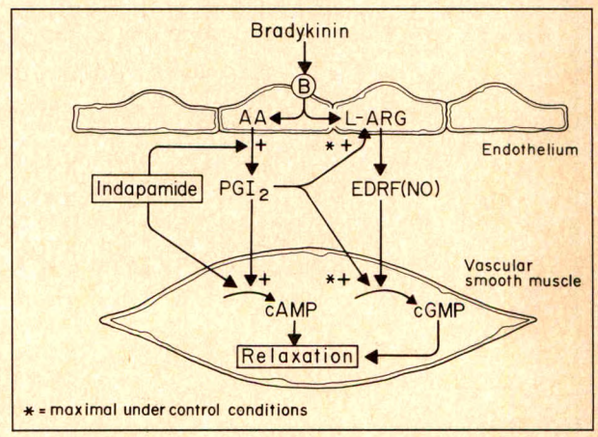


FIGURE 4. Proposed mechanism of action to explain the augmentation by indapamide of the endothelium-dependent relaxations to bradykinin. AA = arachidonic acid; B = bradykinin receptor; EDRF = endothelium-derived relaxing factor(s); cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; L-ARG = L-arginine; NO = nitric oxide; PGI_2 = prostacyclin; + = facilitation.

indapamide restored the inhibited release of prostacyclin or other prostanoids that feed back on the release of, and interact synergistically with, endothelium-derived relaxing factor(s) (Fig. 4).

In the porcine coronary artery, prostacyclin not only facilitates the release of endothelium-derived relaxing factor(s) but also eases its action on vascular smooth muscle.[30] These properties of prostacyclin may be due to activation of adenylate cyclase, since forskolin, a direct activator of the enzyme, has similar effects. The present study demonstrates that indapamide enhances the relaxations evoked by forskolin in rings without endothelium. Thus, it can facilitate either the production or the intracellular effect of cyclic adenosine monophosphate (Fig. 4). However, it is unlikely that this action contributes in a major way to the augmentation of the response to bradykinin. The relaxations evoked by prostacyclin in rings without endothelium were increased only by indapamide. In contrast, the drug significantly increased the relaxations induced by prostacyclin in rings with endothelium. This implies that the potentiating effect on the bradykinin-induced relaxation involves mainly the facilitation of a positive feedback exerted by prostacyclin (or another prostanoid) on the release of endothelium-derived relaxing factor(s) (Fig. 4).

REFERENCES

1. Chaffman M, Heel RC, Brogden RN, Speight TM, Avery GS. Indapamide, a review of its pharmacodynamic properties and therapeutic efficacy in hypertension. *Drugs 1984;3:189–235.*

2. Finch L, Hicks PE, Moore RA. The effects of indapamide on vascular reactivity in experimental hypertensive animals following treatment with indapamide. *J Pharm Pharmacol 1977;29:739–743.*

3. Finch L, Hicks PE, Moore RA. The effects of indapamide on vascular reactivity in experimental hypertension. *Curr Med Res Opin 1977;5:suppl 1:44–54.*

4. Kraetz J, Criscione L, Hedwall PR. Dissociation of the vascular and natriuretic effects of diuretic agents. *Naunyn Schmiedebergs Arch Pharmacol 1978; 302:suppl:R42.*

5. Kyncl J, Oheim K, Seki T, Solles A. Anti-hypertensive action of indapamide. Comparative studies in several experimental models. *Arzneimittelforschung 1975;25:1491–1495.*

6. Uhlich E, Troger C, Knoll W. Effects of indapamide in hypertensive patients and on experimental vascular reactivity. *Curr Med Res Opin 1977;5:suppl 1:71–78.*

7. Usui H, Kanda M, Osumi S, Seki T, Toda N. Influence of indapamide on isolated rabbit arteries. *Folia Pharmacol Jpn 1978;74:389–396.*

8. Mironneau J. Indapamide-induced inhibition of calcium movement in smooth muscles. *Am J Med 1988;84:10–14.*

9. Mironneau J, Gargouil Y-M. Action of indapamide on excitation-contraction coupling in vascular smooth muscle. *Eur J Pharmacol 1979;57:57–67.*

10. Mironneau J, Savineau JP, Mironneau C. Compared effects of indapamide, hydrochlorothiazide and chlorthalidone on electrical and mechanical activities in vascular smooth muscle. *Eur J Pharmacol 1981;75:109–113.*

11. Mironneau J, Savineau JP, Mironneau C. Effect of indapamide on the electromechanical properties of rat myometrium and rat portal vein. *J Pharmacol Exp Ther 1985;236:519–525.*

12. Furchgott RF. Role of the endothelium in response of vascular smooth muscle. *Circ Res 1983;53:557–573.*

13. Vanhoutte PM, Rubanyi GM, Miller VM, Houston DS. Modulation of vascular smooth muscle contraction by the endothelium. *Annu Rev Physiol 1986;48:307–320.*

14. Vanhoutte PM. Endothelium and control of vascular function. *Hypertension 1989;13:658–667.*

15. De Mey JG, Vanhoutte PM. Role of the intima in cholinergic and purinergic relaxation of isolated canine femoral arteries. *J Physiol (Lond) 1981;316:347–355.*

16. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature 1981;288:373–376.*

17. Gruetter CA, Gruetter DY, Lyon JE, Kadowitz PJ, Ignarro LJ. Relationship between cyclic guanosine 3′:5′-monophosphate formation and relaxation of coronary arterial smooth muscle by glyceryltrinitate, nitroprusside, nitrite and nitric oxide: effects of methylene blue and methemoglobin. *J Pharmacol Exp Ther 1981;219:181–186.*

18. Ignarro LJ, Lippton H, Edwards JC, Baricos WH, Hyman AL, Kadowitz PJ, Gruetter CA. Mechanism of vascular smooth muscle relaxation by organic nitrates, nitroprusside and nitric oxide: evidence for the involvement of s-nitrosothiols or active intermediates. *J Pharmacol Exp Ther 1981;218:739–749.*

19. Ignarro LJ, Harbison RG, Wood KS, Kadowitz PJ. Activation of purified soluble guanylate cyclase by endothelium-derived relaxing factor from intrapulmonary artery and vein: stimulation by acetylcholine, bradykinin and arachidonic acid. *J Pharmacol Exp Ther 1986;237:893–900.*

20. Janczewski P, Boulanger C, Iqbal A, Vanhoutte PM. Endothelium-dependent effects of carteolol. *J Pharmacol Exp Ther 1988;247:590–595.*

21. Mostaghim R, Maddox YT, Ramwell PW. Endothelial potentiation of relaxation response to beta-adrenoceptor blocking agents. *J Pharmacol Exp Ther 1986;239:797–801.*

22. Vanhoutte PM, Auch-Schwelk W, Biondi ML, Lorenz RR, Schini VB, Vidal MJ. Why are converting enzyme inhibitors vasodilators? *Br J Clin Pharmacol 1989;28:955–1045.*

23. De Widlt DJ, Hillen FC. A comparative study on possible calcium antagonistic properties of indapamide and other drugs potentially interfering with calcium transport in isolated vascular smooth muscle. *Eur J Pharmacol 1984;102:401–410.*

24. Rimele TJ, Vanhoutte PM. Effects of inhibitors of arachidonic acid metabolism and calcium entry on responses of acetylcholine, potassium and norepinephrine in the isolated canine saphenous vein. *J Pharmacol Exp Ther 1983;225:720–728.*

25. Crutchley DJ, Ryan JW, Ryan US, Fisher GH. Bradykinin-induced release of prostacyclin and thromboxanes from bovine pulmonary artery endothelial cells. *Biochim Biophys Acta 1983;751:99–107.*

26. Whorton AR, Young SL, Data JL, Barchowsky A, Kent RS. Mechanism of bradykinin-stimulated prostacyclin synthesis in porcine aortic endothelial cells. *Biochim Biophys Acta 1982;712:79–87.*

27. Katusic ZS, Shepherd JT, Vanhoutte PM. Endothelium-dependent contractions to calcium ionophore A23187, arachidonic acid and acetylcholine in canine basilar arteries. *Stroke 1988;19(4):476–479.*

28. Miller VM, Vanhoutte PM. Endothelium-dependent contractions to arachidonic acid are mediated by products of cyclo-oxygenase in canine veins. *Am J Physiol 1985;248:H432–H437.*

29. Luscher TF, Vanhoutte PM. Endothelium-dependent contractions to acetylcholine in the aorta of the spontaneously hypertensive rat. *Hypertension 1986;8:344–348.*

30. Shimokawa H, Flavahan NA, Lorenz RR, Vanhoutte PM. Prostacyclin releases endothelium-derived relaxing factor and potentiates its action in porcine coronary artery. *Br J Pharmacol, 1988;95:1197–1203.*

31. Gbeassor FM, Grose JH, Lebel M. Influence of diuretics on prostaglandin and thromboxane synthesis. *Clin Invest Med 1983;5:26B.*

32. Lebel M, Grose JH, Belleau LJ, Langlois S. Antihypertensive effect of indapamide with special emphasis on renal prostaglandin production. *Curr Med Res Opin 1983;8:suppl 3:81–86.*

Cardiovascular Protective Properties of Indapamide

D. Bruce Campbell, PhD, and François Brackman, MD

Although indapamide has been used for many years as a first-line treatment of hypertension, it is only recently that some of its activities on the changes of the cardiovascular system, brought on by age and high blood pressure, have been studied. Indapamide appears to reduce blood pressure by a combined diuretic and direct vascular activity reducing vascular reactivity and total peripheral resistance. In addition, it has discrete effects on a number of interrelated systems that may protect the cardiovascular system. Indapamide reduces intracellular calcium levels, maintains magnesium ions, but reduces phosphate ions that may be involved in arterial rigidity. Circulating catecholamines remain unchanged but there is a reduction in normetanephrine, suggesting a reduction in sympathetic tone. It stimulates prostacyclin synthesis, increases levels of circulating prostacyclin, reduces platelet aggregation and stimulates the vasodilation elicited by endothelium-derived relaxing factor in the presence of bradykinin. In addition, it inhibits the formation of the vasoconstrictor prostanoid, thromboxane A_2. The free radical scavenging activity of indapamide could also protect the vascular smooth muscle from the reperfusion injury of cerebral and myocardial ischemia. Indapamide induces a reduction in cerebral ischemia after carotid ligation. Unlike some other antihypertensives, it does not upset the high-density/low-density lipoprotein-cholesterol balance, reducing the possible risk of atherosclerosis. Moreover, the combination of binding to elastin and reduction in uptake of calcium and phosphate into the smooth muscle could be a mechanism for reducing arterial rigidity seen in the elderly and hypertensive patient. In hypertensive patients, these properties induce an improvement in arterial compliance, and in the long term a reduction in left ventricular hypertrophy. These pharmacologic and clinical results, together with a good antihypertensive efficacy and acceptability, suggest that indapamide may be a preferential agent in the long-term cardiovascular protection of the hypertensive patient.

(Am J Cardiol 1990;65:11H–27H)

The role of hypertension in cardiovascular prognosis is well established, and many population studies have confirmed that high blood pressure is associated with a higher incidence of cerebrovascular accidents, coronary artery disease and left ventricular hypertrophy. Consequently, reduction of blood pressure to normal values in order to decrease both the incidence and the severity of cardiovascular complications appears to be clinically relevant. Several long-term prospective studies, including thousands of patients treated for years, have been conducted to confirm this hypothesis, but most of them showed only partial results when considering global cardiovascular prevention. Whereas the incidence of cerebrovascular complications was significantly reduced, the effect on coronary artery disease was incomplete, with little or no reduction in myocardial infarction; it has been suggested that this might be due to the deleterious effects of the agents on some risk factors other than high blood pressure. Whatever the reason for such results, this shows that the cardiovascular prognosis is not solely controlled by blood pressure values and that the choice of an antihypertensive agent should also be based on its mechanism of action and on its effects on other cardiovascular risk factors.

In this respect, indapamide, an antihypertensive agent with minimal diuretic activity and specific vascular effects, seems to present many of the known properties required for an optimal cardiovascular protection. Indapamide is available in more than 100 countries, including Japan and the United States, and is being used daily by 1.5 million hypertensive patients, some of these having been treated for more than 5 years. More than 600 publications on animal experiments, clinical pharmacology studies and long-term therapeutic trials have provided us with an extensive knowledge of the vascular activity of indapamide, its antihypertensive action and its effects on all the factors involved in cardiovascular progress, from cellular properties to long-term effect on lipids and left ventricular hypertrophy.

This review, while summarizing the main results available in these fields, attempts to evaluate their possible consequences on the long-term cardiovascular prognosis of the hypertensive patient treated with indapamide.

From Servier Research and Development Limited, Fulmer Hall, Windmill Road, Fulmer, Slough SL3 6HH, England; IRIS, Neuilly-sur-Seine, Paris, France.

Address for reprints: D. Bruce Campbell, PhD, Servier Research and Development Limited, Fulmer Hall, Windmill Road, Fulmer, Slough SL3 6HH, England.

TABLE I The Cardiohemodynamic Activities in Indapamide

Reference	No. of Pts.	Treatment (weeks)	BP (Δ%)	HR (Δ%)	CO (Δ%)	TPR (Δ%)	MBF (Δ%)	Methods[a]
17	20	8				−27*[b]		
23	5	6					+53*[c]	
24	10	1.5	−17*	+1	−5	−12*	+27* +47*[d]	Radiocardiogram (SARI)
18	9	6	−12*	+1	+2	−15*	+21*	Cardiac impedance
19	9	6	−7*	+6*	+12*	−17*		M-mode echocardiography
20	11	12	−15*	+2		−19*	+14	
21	10	8	−12*	−6	−9	−3*		Thermodilution
26	6	4	−10	+6		−27	+80*	
22	8	1.5	−16*	0	0	−19*		Thermodilution
15	10	12	−12*	+3	+12*	−26*		Cardiogreen dilution
14	9[e]	4	−15*	+6	−9*			M-mode echocardiography
	6[f]	4	0	+11	−5			
Mean ± SD	9 ± 4	6 ± 4	−13 ± 3	9 ± 4	0.5 ± 8.9	−18 ± 8	39 ± 27	

* $p < 0.05$.
[a] Methods for measurement of cardiac output: unless otherwise stated, all methods for blood flow were plethysmography.
[b] Measured by carotid pulse waves.
[c] Measured by xenon washout.
[d] After exercise.
[e] Responders whose blood pressure was reduced.
[f] Nonresponders.
BP = blood pressure; CO = cardiac output; HR = heart rate; MBF = muscle blood flow; SD = standard deviation; TPR = total peripheral resistance.

VASCULAR ACTIVITY

The mechanism by which indapamide decreases blood pressure has been the subject of much discussion, since it appears to have both diuretic activity and vasoactivity.[1–3] The diuretic activity in terms of plasma, sodium, potassium and uric acid levels, body weight and plasma volume changes are less than half those found for medium-dose thiazide diuretics.[4] Conversely, indapamide does appear to have a direct effect in vitro on isolated vascular smooth muscle to inhibit contractions elicited by norepinephrine, epinephrine, angiotensin II[5–7] and prostaglandin F_2 (PGF_2)[8]; the effect of indapamide is dose dependent and is not observed with trichloromethiazide.[7] In addition, indapamide, in contrast to hydrochlorothiazide, reduces in vivo the vascular reactivity to norepinephrine, tyramine, angiotensin II, and electrical stimulation of the entire sympathetic outflow in rats.[9,10] Similarly, in humans, indapamide, after 2 to 12 weeks, significantly reduces vascular reactivity by increasing the doses of norepinephrine, angiotensin II or phenylephrine by 30 to 120% needed to increase blood pressure by 10 to 20 mm Hg.[11–15] Interestingly, the reduction in vascular reactivity achieved by indapamide was found to be linearly related ($r = -0.62$, $p < 0.05$) to the mean initial blood pressure of the subjects treated.[12]

Further evidence that indapamide may have an independent vascular activity is the finding that there is a reduction in blood pressure in patients ($n = 9$) who are functionally anephric, an activity that cannot be affected by diuresis.[16] Indapamide reduces blood pressure by significantly reducing total peripheral resistance (mean −18%, range −3 to −27%),[15,17–22] by increasing muscle blood flow (mean +39%, range 14 to 53%)[18,20,23,24] without reflexly increasing heart rate, possibly because of vasodilation on both veins and arteries or by a resetting of the baroreceptor reflex[25] (Table I).

IONIC TRANSPORT

Calcium: Although it is evident from cardiohemodynamic studies that the major effect of indapamide is to reduce total peripheral resistance, the exact mechanism of this activity is unclear. Early electrophysiologic studies suggested that there was a dose-dependent reduction in the phasic contraction elicited by the inward flow of calcium ions into vascular smooth muscle[27] and that this activity was 4 and 50 times more active than hydrochlorothiazide and chlorthalidone, respectively, in polarized and depolarized rat portal vein (Fig. 1).[28] Concentrations that achieve these reductions of 10 to 25% in contraction fall within the human therapeutic range of blood and vascular smooth muscle concentrations.

In addition, there appears to be a secondary effect on blocking the release of calcium from norepinephrine-sensitive and peripheral sarcoplasmic reticulum stores, but indapamide does not facilitate the calcium reuptake into these stores.[29] Other techniques, such as measuring the movement of radioactive calcium across the rat aorta, have confirmed the inhibitory activity on calcium transport.[30]

Recently, more detailed studies[31] have shown that indapamide, up to 10 μmol/liter, has little activity on the fast inward calcium current but inhibits the slow current. Calcium channels exist in 3 conformational states depending on their activation: open, resting and inactivated. In contrast to calcium antagonists, indapamide binds to the resting channels, whereas verapamil binds to open channels and nifedipine to inactivated channels. It is unclear what this means therapeutically but the type of activity may confer on the molecule some degree of selectivity on different vascular tissues. Indapamide, however, is up to 500 times less potent than nifedipine and this may be why indapamide does not cause the acute side effects of the calcium vasodilators, such as orthostatic hypoten-

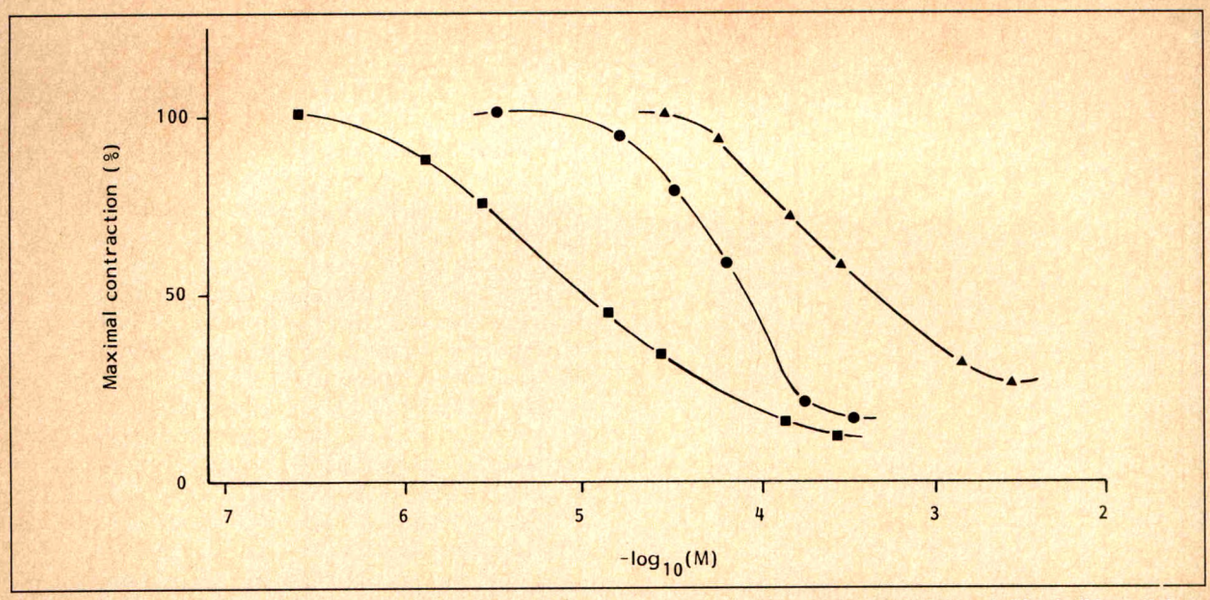


FIGURE 1. Dose response curves for the effect of indapamide (*squares*), hydrochlorothiazide (*circles*) and chlorthalidone (*triangles*) on triggered isometric contractions in polarized rat portal vein (n = 5).[28] (Modified from Mironneau et al, 1981.)

sion, flushing and increased heart rate, but has a more gradual action on reduction of blood pressure without acutely disrupting physiologic control systems. Even so, the concentrations (80 nmol/liter) that produce a 50% inhibition of the calcium current are comparable to therapeutic plasma steady-state concentrations, 200 ng/ml, found in whole blood.[1]

Phosphate: Although there has been much discussion on the role of sodium and calcium transport in the development and maintenance of high blood pressure, little attention has focused on the importance of phosphates in the pathophysiology of arterial hypertension. A few studies have suggested that phosphate metabolism may be important. In a large epidemiologic study performed 12 years ago, Ljunghall and Hedstrand[32] found that serum phosphate concentrations were inversely related to both systolic and diastolic pressures in normal subjects. More recently, Gruchow et al[33] showed that systolic blood pressure increased with higher dietary phosphate ingestion. Pharmacologic studies have also suggested that there are alterations in phosphate metabolism in spontaneously hypertensive rats,[34] and that long-term phosphate depletion in normal rats leads to an important improvement in vascular reactivity to various pressor amines.[35] It was

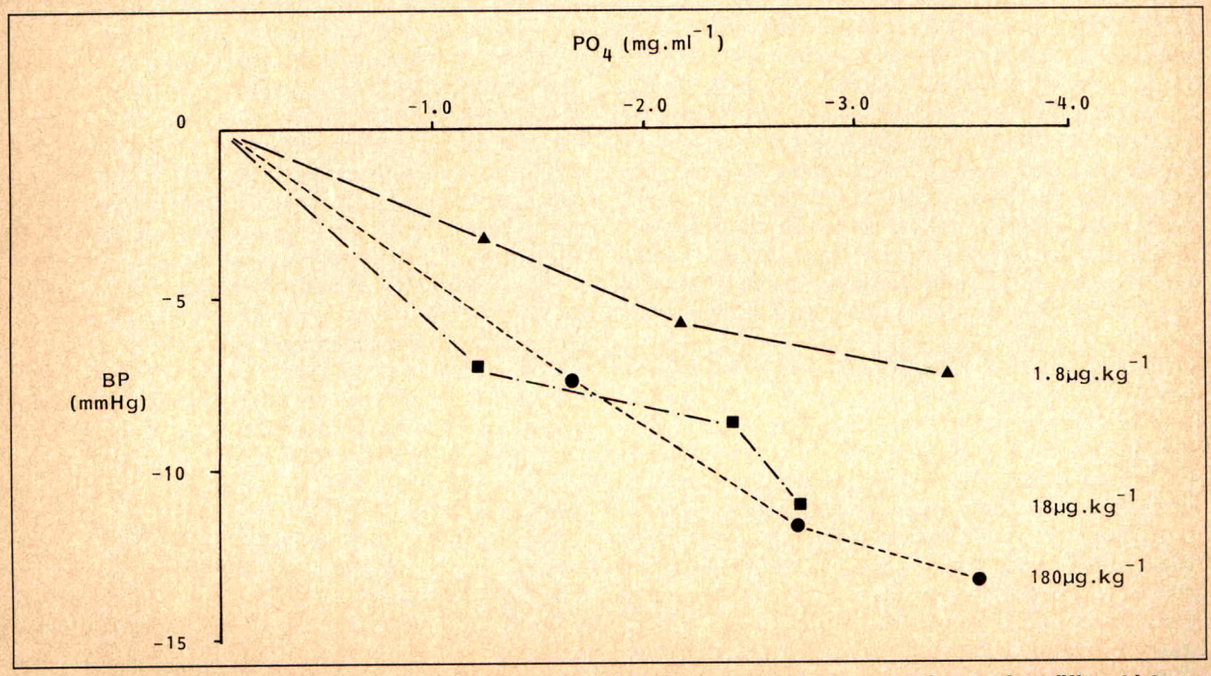


FIGURE 2. The relationship between the reduction in plasma phosphate levels and blood pressure in rats given different intravenous doses of indapamide with measurements taken up to 60 minutes after dosing.[38] (Modified from Plante, 1988.)

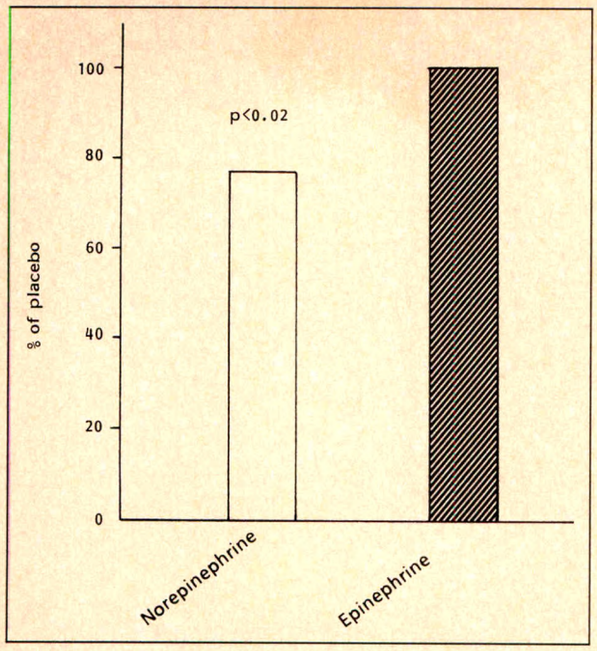


FIGURE 3. Comparison of the change in circulating catecholamine levels compared with placebo in patients treated with indapamide, 2.5 mg/day, for 3 months.[25] (Modified from Caretta et al, 1988.)

therefore of some interest to find that, unlike thiazide diuretics, indapamide, although at diuretic doses, was found to increase the renal excretion of phosphate and subsequently to reduce vascular reactivity.[36] Further studies on rats, in which lower, nondiuretic doses (1.8 to 180 μg/kg intravenously) were used, confirmed that indapamide significantly increased the fractional phosphate excretion up to 68%.[37] This action was considerably more marked than the relatively weak effect of indapamide on fractional sodium excretion where only a maximal 4% incremental change was found. In addition, there was a reduction of inorganic phosphate in kidney cortex and skeletal muscle by approximately 50% and plasma phosphate levels up to 35%. Only small, nonsignificant reductions in plasma, calcium and sodium were observed. The finding that these reductions in plasma phosphate are directly related to the reductions in blood pressure (Fig. 2) and that similar results have been found in hypertensive patients[38] raises the question of the importance of phosphate levels in the control patient with arterial hypertension.

In humans, high doses of indapamide, 40 mg, increased urinary excretion of phosphate,[39] but significant changes were not seen at lower doses administered for 1 week[40] or longer.[41] Unfortunately, changes in phosphate metabolism have rarely been documented for other antihypertensive treatments, but where it has been measured, as in the case of hydrochlorothiazide, the reduction in blood pressure has not been accompanied by a change in phosphate levels. It is too early to say how important these findings are, whether they are specific to indapamide, or whether this is an important action of the drug. Clearly, more work needs to be done, but, as will be discussed later, phosphate may also be involved in the decreased elasticity of compliance vessels, as seen in the elderly as a result of calcium hydroxyphosphate deposition in association with elastin.

Magnesium: Physiologically, magnesium is similar to potassium and most is reabsorbed in the kidney. Total body stores do not reflect plasma concentrations and both are required at critical levels to prevent cardiac arrhythmias.[42] Most diuretics stimulate renal excretion and lower plasma levels of magnesium, thereby predisposing the heart to abnormal rhythms when concentrations decrease excessively.[43] Indapamide, at the high dose of 40 mg, increased the urinary excretion of magnesium, and serum levels decreased.[39] However, at the therapeutic dose, unlike most diuretics tested, indapamide did not modify 24-hour urinary magnesium.[44] Unfortunately, magnesium serum levels are rarely measured in clinical studies after long-term administration, but they remained unchanged after treatment for 3 months[45] and in patients treated for up to 2 months with renal disease.[16] If this is confirmed in future studies, this conservation of magnesium may be a beneficial activity of indapamide.

BLOOD PRESSURE CONTROL

There is increasing evidence that blood pressure is not only controlled by the heart and the central nervous system, but also more directly in terms of vascular tone. This evidence includes a variety of locally acting vasodilating and vasoconstricting substances, some produced by the endothelium, including prostaglandins, endothelium-derived relaxing factor (EDRF), endothelium-derived constricting factor, local autacoids like bradykinin, histamine, substance P, circulating compounds like the catecholamines, vasopressin, oxytocin, atrial natriuretic polypeptide (ANP), or platelet-derived products such as adenosine phosphate, serotonin and thrombin. Although the physiologic role and the mechanism in which each factor interacts are not fully understood, it is clear that these agents may have a greater fundamental role in vascular tone than previously considered, particularly in the "fine tuning" of blood pressure on a minute-to-minute basis. It is therefore important to know, when treating hypertension, how a medicine interacts with the turnover of these regulatory substances and to see if some of the activity could be mediated, at least in part, by them.

Circulating pressor substances: Diuretics and powerful vasodilators like hydralazine have been shown to increase both plasma and urinary catecholamines by a reflex stimulation of sympathetic nerve tone.[46,47] Although, overall, indapamide does not appear to change circulating plasma levels of either norepinephrine or epinephrine, there is an interstudy variability with some studies finding small increases (+8%)[12,48,49] and others finding decreases of −23%[25] (Fig. 3) and −7%.[50]

Similarly, urinary norepinephrine may be increased.[12,49] The finding that plasma normetanephrine, reflecting the release of "active" norepinephrine from nerve endings, was reduced by 23% suggests that indapamide may have a sympathoplegic effect, reducing sympathetic catecholamine turnover.[49]

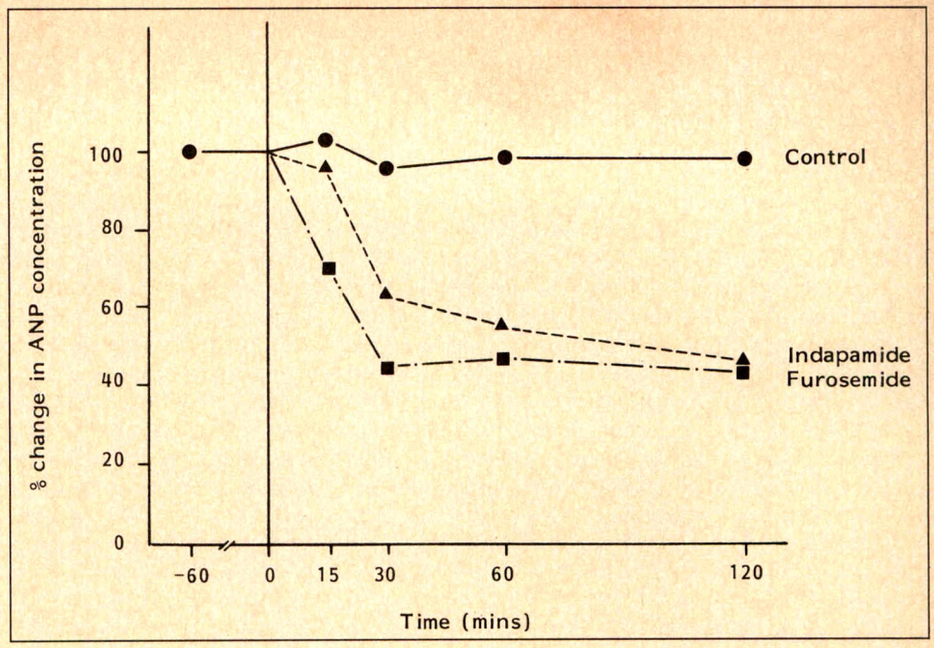


FIGURE 4. Comparison of the percentage change in plasma atrial natriuretic peptide (ANP) concentrations after administration of indapamide (16.5 mg/kg, intraperitoneally) and furosemide (1.6 mg/kg, intravenously) in normotensive rats.[73] (Modified from Oliver et al, 1988.)

Indapamide, like the diuretics and calcium antagonists, approximately doubles plasma renin activity,[4] and, with a concomitant increase in aldosterone,[11,51,52] reflects angiotensin II synthesis. This effect would blunt the antihypertensive activity, producing the flat dose-response curve observed with these drugs, and provides a rationale for the enhanced therapeutic efficacy when combined with angiotensin-converting enzyme (ACE) inhibitors.

Endothelium-derived factors: From the initial work of Furchgott and Zawadski,[53] who showed that the presence of an intact endothelium was necessary to produce vasodilation of the underlying vascular smooth muscle by acetylcholine, the role of EDRF in maintaining vascular tone has been established.[54,55] Such endothelium-dependent vasodilation occurs in all vascular tissue and in most animal species, including reptiles, suggesting a primitive evolutionary origin.[56] Although EDRF may be a mixture of compounds,[57] the major component seems to be identical to nitric oxide.[58,59] It is interesting that nitric oxide is also the active metabolite of the nitrovasodilators, acting, as does EDRF, through stimulation of soluble guanylate cyclase, raising levels of cyclic guanosine monophosphate (GMP) and reducing intracellular free calcium.[60] However, it is very unstable with a half-life of approximately 30 seconds, and is inactivated by oxygen-free radicals.

Inadapamide, in combination with indomethacin to eliminate the involvement of prostaglandins, significantly augments the endothelial-dependent vasorelaxation effects of bradykinin and adenosine diphosphate in canine femoral arteries when the endothelium is contracted with prostaglandin $F_{2\alpha}$.[55]

This effect cannot be explained by a direct release of EDRF, and further work has shown that this is probably an indirect action through the release of prostacyclin from the endothelium which can, by a positive feedback mechanism, modulate the activity of EDRF and GMP through an enhancement of intracellular cyclic AMP.[61] How important this mechanism of action is for the blood pressure–reducing properties of indapamide is not known, but certainly there are suggestions that EDRF or the lack of it may be implicated in clot formation, myocardial infarction, lipid deposition and atheroma, coronary vasospasm, subarachnoid hemorrhage, and the modulation of the vascular smooth muscle, particularly in resistance vessels,[62] although much of this work has been undertaken in animals. More recently, in vivo studies have shown that EDRF does play an important role in the control of venous tone in humans.[63]

Atrial natriuretic polypeptide: Although, for many years, morphologists of atrial cells had observed secretory granules,[64,65] it was a further 20 years before the active components were identified as a class of polypeptides known as atrial natriuretic factor or peptide.[66] Within a few years, the peptide was isolated[67] and the amino acid sequence determined,[68] synthesized[69] and finally cloned.[70] The remarkable fact about this compound is that although there is a large amount of information on its identity, its location, and its basic properties of vasorelaxation, diuresis and natriuresis, its precise mode of action is poorly understood. It seems to act as an antiangiotensinogenic, as the body's natural diuretic hormone, by counteracting the aldosterone-renin-angiotensin system, since it inhibits aldosterone synthesis, renin and vasopressin release.[71] Although the mechanism by which ANP is released from the heart remains unresolved, it is thought to occur during atrial distension, since there is an elevation of plasma ANP levels under conditions when this occurs, such as cardiac failure[72] or tachyarrhythmias.[73] ANP receptors have been located in brain, adrenals, renal tubules and blood vessels, and it is probable that it acts through the second messenger, GMP, within the cell. Certainly, there is a significant increase in GMP in blood

and urine when ANP is injected peripherally.[74] The exact role of ANP in the control of blood pressure is unknown, but there is accumulating evidence that, in association with many other transmitters and hormones, it may be important, since levels are often elevated in hypertensive patients. Intravenous infusions in both normal volunteers and hypertensive patients reduce blood pressure and heart rate in some[75] but not all,[76] but diuresis and natriuresis occurred in both groups and were exaggerated in the hypertensive patients. Although there were no significant changes in plasma renin activity, dopamine and epinephrine, there were significant increases in aldosterone, epinephrine and hemoconcentration in both groups, but only an increase in plasma arginine-vasopressin in the hypertensive patients. Taken together, these results suggest that ANP may play an important role in body fluid homeostasis, with extravascular fluid shifts,[77] diuresis and natriuresis, but with higher ANP levels leading to volume expansion and hypertension. Conversely, ANP may also reduce blood pressure by a direct action on vascular smooth muscle.[75]

Indapamide has recently been shown to interact with ANP metabolism. When spontaneously hypertensive rats were given indapamide for 10 days (10 mg/kg), blood pressure was reduced but with no change in plasma levels of urea, creatinine, sodium or chloride. However, there was a change in the ANP receptor binding in the kidney measured by the specific binding of ^{125}I-ANP.[78] In comparison with nontreated hypertensive controls, there was an increased affinity for ANP binding sites after indapamide treatment but with a reduction in maximal binding. This latter effect may be due to a down-regulation of receptors caused by the hypotensive activity of the drug. In another study, indapamide was compared with furosemide after acute and long-term treatment (3 weeks). Both drugs, after single doses, caused an immediate decrease in ANP levels but without a change in the intravascular volume or hematocrit (Fig. 4).[73] This reduction in ANP was thought to be due to a reduction in arterial distension brought about by a decrease in cardiac preload together with a change in peripheral capacitance as a consequence of the vasodilation of vascular smooth muscle.

However, after long-term treatment in this study at high doses, 33.3 mg/kg indapamide and 1.6 mg/kg furosemide, there was no change in atrial levels of ANP, nor were there any differences in receptor binding on the kidney as shown by autoradiography. It is apparent that more work is needed in this area to see how indapamide and other drugs, during long-term treatment at hypotensive doses, may modify the ANP levels and activity, and how important this peptide is in causing vascular distension or in merely indicating that it has occurred.

CARDIOVASCULAR PROTECTION

We are becoming increasingly aware that the body has many interrelated systems that protect the cardiovascular system against damage. Under normal situations (e.g., to stop bleeding), platelet aggregation leads to thrombus formation to form a cellular plug at the site of vessel injury. Inappropriate thrombus formation, on the other hand, in an atherosclerosed coronary artery, will lead to myocardial infarction and death. The production of oxygen-free radicals by leukotrienes in granulocytes disrupts the cell membranes of invading organisms and is part of the normal defense mechanism against infection. Unfortunately, as the body gets older and diseases occur, the granulocytes mistake small lesions in vessels or organs for foreign protein and attempt to remove them by their phagocytic mechanism, thereby further damaging the tissue. This is certainly a concern in cardiovascular disease, in which antihypertensive drug therapy, although significantly reducing the incidence of strokes, has had little clearly demonstrable effect on coronary artery disease.[79,80] In this case, the progression of platelet aggregation, microthrombi, lipid deposition, plaques, atherosclerosis, and rigidity and narrowing of vessel wall leads to a reduced blood flow, hypoxia, reperfusion-free radical damage on one hand, or the regrowth and proliferation of damaged vascular and endothelial cells, with subsequent inefficient protection by the new endothelium, on the other. Clearly, any antihypertensive agent that not only decreases blood pressure, but also provides some protection against these pathologies may have distinct advantages.

Prostaglandins: The role of prostaglandins and, in particular, prostacyclin and thromboxane A_2, in the control of homeostasis is now well established. Any antihypertensive treatment that at least maintains or actually enhances the antithrombotic and vasorelaxant activity of the prostaglandins is desirable. At low doses (3×10^{-8} mol/liter) in vitro indapamide significantly increases the synthesis of prostacyclin in sheep seminal vesicle microsomes, whereas furosemide, and hydrochlorothiazide at doses up to 10^{-4} mol/liter, had only a weak activity; spironolactone, in contrast, inhibited prostacyclin synthesis.[81] In addition, indapamide inhibited the synthesis of thromboxane A_2 from human platelet microsomes, whereas the other compounds weakly stimulated its synthesis.[82] In spontaneously hypertensive rats, Izumi et al[83] and Honda et al[84] also showed that as indapamide (2 mg/kg/day administered orally for 2 weeks) reduces blood pressure, particularly after 7 days, there is a concomitant significant increase in the urinary excretion of 6-keto $PGF_{1\alpha}$, a stable metabolite of prostacyclin (Fig. 5). This suggests that alterations in the prostanoid turnover may be involved in the antihypertensive action of indapamide, possibly by reversing the decrease in synthesis of prostacyclin from the vascular smooth muscle of hypertensive animals.[85] Recently, Numabe et al[86] confirmed these findings using cultured vascular smooth muscle cells from the aorta of spontaneously hypertensive rats. Indapamide at physiologic concentrations increased the synthesis of the vasorelaxant 6-keto $PGF_{1\alpha}$ by 7% at 10^{-7} mol/liter and significantly by 21% at 10^{-5} mol/liter. Thromboxane A_2 release was reduced at all concentrations from 10^{-9} to 10^{-5} mol/liter by approximately 13% but this did not reach statistical significance.

In contrast, furosemide and the thiazide trichloromethazide reduced $PGF_{1\alpha}$ synthesis by 13 and 28%, re-

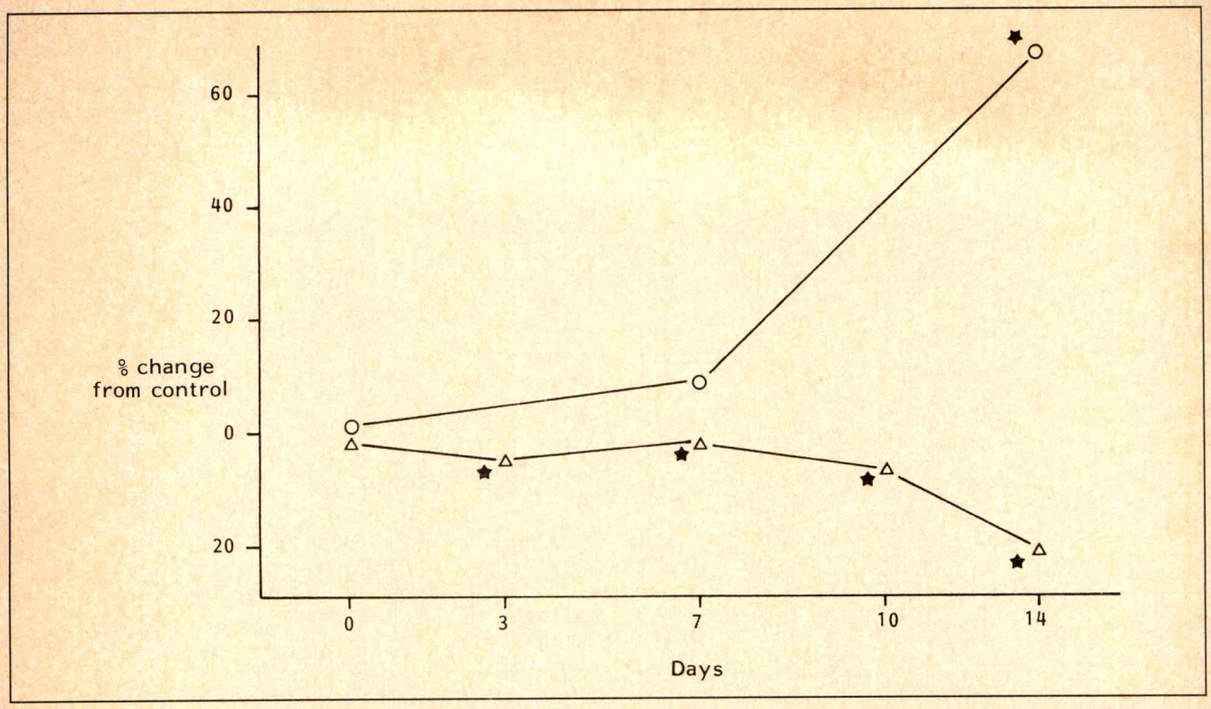


FIGURE 5. The relationship between the decrease in blood pressure (*triangles*) and increase in urinary excretion of 6-keto-$PGF_{1\alpha}$ (*circles*) in spontaneously hypertensive rats (n = 8) receiving indapamide (2 mg/kg/day) for 2 weeks compared with a control group. *p <0.01.[83] (Modifed from Izumi et al, 1986.)

spectively, and increased thromboxane synthesis by 45 and 32%, respectively, at the highest dose (Fig. 6). Similarly, in 11 patients with uncomplicated hypertension successfully treated with indapamide, 2.5 mg daily for 6 weeks, after a 3-week placebo run-in period, there was a 62% increase in the vasodilating prostanoid $PGF_{2\alpha}$ and a significant 43% increase in PGE_2.[52,87] Indapamide also inhibits the contractions elicited by $PGF_{2\alpha}$ in rabbit vascular smooth muscle preparations and the effect was not blocked by atropine, propranolol or aminophylline.[8] It is difficult to know with the available evidence how the prostacyclins fit into the complex interactive regulation of the blood pressure control. They are certainly widely distributed throughout the body, particularly in the lungs and kidney, and are synthesized (especially prostacyclin) in vascular endothelial cells in response to various stimuli including histamine, thrombin and angiotensin II. Their protective effects against platelet aggregation are well established, but their involvement in the control of vascular tone is less clear, although there is increasing evidence of their inhibition of various vasoconstrictor substances like thromboxane A_2 and their positive interaction with EDRF. They probably reduce blood pressure by (1) a direct action of vascular smooth muscles, (2) reducing release of neurotransmitters from nerve endings and vascular responsiveness, (3) stimulating the vasodilator and natriuretic activity of the kinins[88]; and (4) regulation of sodium excretion. They may also increase blood pressure by stimulating renin secretion (PGI_2) and vasoconstriction ($PGF_{2\alpha}$ and thromboxane A_2). Certainly, pretreatment with the cyclooxygenase inhibitor indomethacin, which, among other activities, blocks the formation of prostacyclin, reduces the action of indapamide (Delbarre B, personal communication) and other antihypertensive agents, suggesting a primary role for prostacyclin in the control of blood pressure. It has been reported that part of the hypertensive activity of the loop diuretics may also be mediated by a synthesis of prostanoids from the vessel wall.[89]

Platelets: There is now substantial evidence to implicate platelets as one of the initiating factors in the development of atherosclerosis and myocardial infarction.[90] In addition, hypertension and diabetes lead to a hyperadhesiveness and aggregation, increasing the risk of vascular complications.[91,92] Recently, it has been shown that indapamide, unlike antihypertensive diuretics, may interact in the process of platelet aggregation.[93,94] With use of either human or rabbit platelets, indapamide (2 to 8 $\times$ 10^{-4} mol/liter) has been shown to inhibit phase 2 of the biphasic platelet aggregation induced by epinephrine, collagen, arachidonic acid, thrombin, and, to a lesser extent, adenosine diphosphate, but to have no effect on phase 1 (Fig. 7).

This secondary aggregation is thought to be due to the synthesis of thromboxane A_2, but because indapamide had no effect either on labile aggregation-stimulating subtance (LASS) (a mixture of PGH_2 and thromboxane A_2) formation from arachidonic acid or on malondialdehyde, an indirect measure of the formation of thromboxane A_2, it can be concluded that indapamide is not inhibiting platelet aggregation by inhibiting thromboxane A_2 synthesis. However, in addition, indapamide inhibits the aggregation of LASS and U-46619, a thromboxane A_2 and PGH_2 agonist, and it is possible that indapamide may

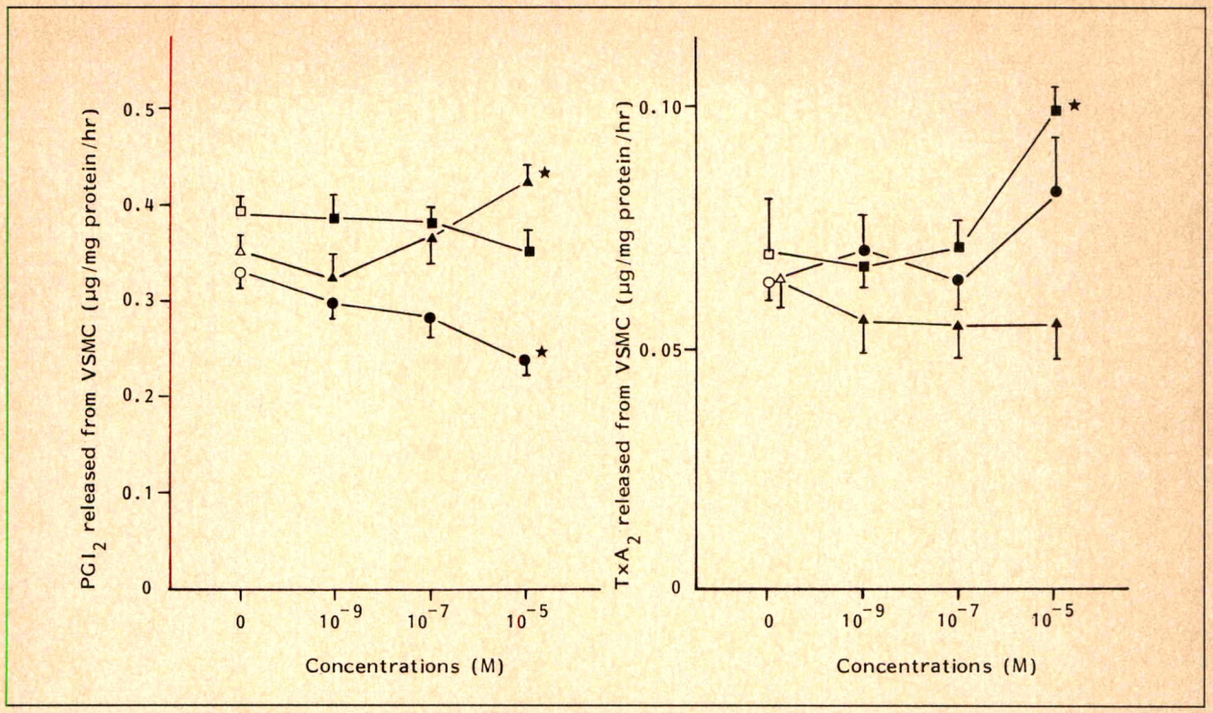


FIGURE 6. Comparison of the release of PGI_2 and thromboxane A_2 from spontaneously hypertensive rat aortic strips after incubation with furosemide (*squares*), trichloromethiazide (*circles*) and indapamide (*triangles*). *p <0.05.[86] TXA_2 = thromboxane A_2; VSMC = vascular smooth muscle cell. (Modified from Numabe et al, 1988.)

act by blocking the thromboxane A_2/PGH_2 receptors, inhibiting calcium uptake, or by enhancing prostacyclin synthesis and release in the platelet. Certainly, recent studies have shown that indapamide may not directly stimulate PGI_2 synthetase activity, per se, but does inhibit the reduction in its activity brought about by the free radical 15-hydroperoxyeicosatetraenoic acid, possibly by its scavenging effects.[96] There is the additional possibility that the reduction of oxygen-free radicals by indapamide may also be involved, because superoxide, but not hydroxyl, anions have been shown to increase platelet adhesion and aggregation.[97] Although the concentrations used in some of these studies are higher than those found in blood and further studies are needed to understand the

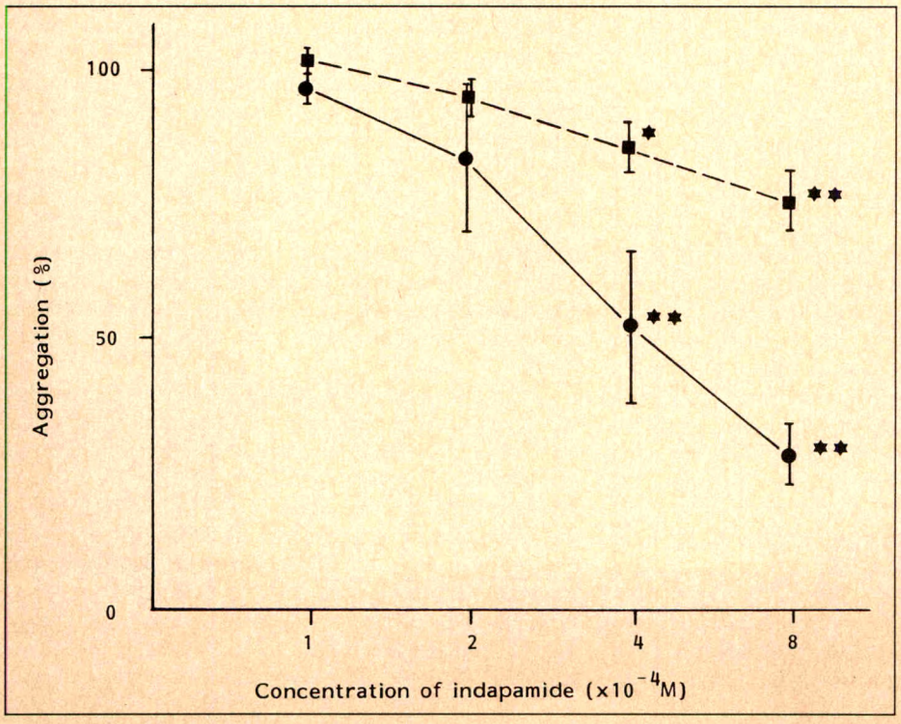


FIGURE 7. The reduction in human platelet aggregation induced by epinephrine (10 µM) (*circles*) or adenosine diphosphate (5 µM) (*squares*) after incubation of various concentrations of indapamide (*p <0.05; **p <0.01).

mechanism of action, this activity of indapamide is of some interest, since the hyperaggregation induced by adenosine diphosphate and epinephrine is present in patients with essential hypertension, possibly because of their more elevated levels of catecholamines.[91]

In addition to their protective activity on vessel leakage, the platelets also contain factors, platelet-derived growth factor, epithelial growth factor and transforming growth factors, which stimulate regeneration of the damaged endothelium. This plasma mitotic activity is enhanced particularly in diabetic subjects, presumably because of continual microangiopathy, but it is also higher in hypertension and with increasing age.[92] This would seem to be a beneficial effect and is useful for isolated lesions. However, when such lesions become frequent, as occurs in disease or aging due to free radical damage, the proliferation of vascular smooth muscle tissue leads to new endothelium which no longer responds to various protective stimuli. Attention has focused on the ways that drugs may alter the levels of these factors within the circulation, particularly those that are currently used in treatment. Thus, insulin normalizes the excessive amounts of growth-promoting activity in platelets from type I patients and hydrochlorothiazide increases the activity in hypertensive rats.[98] Indapamide, however, maintains growth activity in young animals but tends to reduce it in the elderly animals that have higher activity. In hypertensive diabetic patients treated for 3 months, indapamide did not modify growth activity, whereas an increase occurred with hyudrochlorothiazide.[99] This is another aspect of cardiovascular pharmacology that should be considered when choosing antihypertensive therapy, because continual regrowth leads, among other problems, to basement membrane thickening and eventual renal disease.

Indapamide also increases the number of α_2 platelet receptors without altering the dissociation constant or binding affinity.[100] Although the exact mechanism and consequence of this effect is unclear, it is unlikely to be a nonspecific activity of blood pressure reduction, since not all antihypertensive drugs have this effect. It is more likely to be a result of reduction in sympathetic tone as indicated by the reduction of norepinephrine levels and enhancement of baroreceptor sensitivity found by these investigators.[25]

Lipids: The reduced ratio of high-density lipoprotein (HDL) to low-density lipoprotein (LDL) cholesterol in the formation of atherosclerosis and subsequent coronary artery disease is well known, and in major countries throughout the world, educational advice is being given to reduce the dietary intake of foodstuffs containing saturated fats. Because antihypertensive therapy may only marginally improve coronary artery disease, it is essential that the drugs used to reduce blood pressure do not exacerbate the situation by reducing the protective HDL/LDL ratio. Although still open to some discussion, nonselective β blockers with no intrinsic sympathomimetic activity (ISA) appear to decrease the HDL/LDL ratio by reducing HDL levels, whereas selective drugs with ISA and the α blocker prazosin increase the ratio by decreasing LDL and increasing HDL concentrations.[101,102] Calcium antagonists, ACE inhibitors and methyldopa do not appear to change the ratio.[102] Similarly, it appears from the many studies undertaken with indapamide, in patients treated from 3 to 24 months, that there is no change in either the levels of HDL and LDL cholesterol or triglycerides.[103–105]

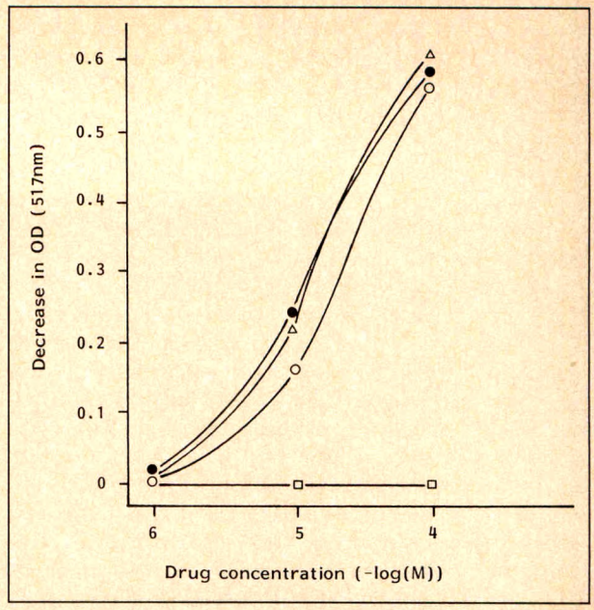


FIGURE 8. The quenching of the stable free radical 1,1-diphenyl-2-picrylhydrazyl by different concentrations of indapamide (*open circles*), 5-hydroxy-indapamide (*closed circles*), α-tocopherol (*triangles*) and trichloromethazide (*squares*).[108] (Modified from Tamura et al, 1987.)

Oxygen-free radicals: The formation of the highly reactive, but short-lived, species of oxygen called the superoxide or oxygen-free radical, with its added orbital electron, has now been implicated in many diseases and cardiovascular problems, including reperfusion injury to vascular and cardiac smooth muscles, atherosclerosis, adult respiratory distress syndrome, renal failure, arthritis, and general aging of the body. Although they may have several activities, e.g., acting as a messenger to attract granulocytes, the main effect is to induce lipid peroxidation of the unsaturated fats within the phospholipids of the cell membrane. Such damage to the cell wall causes leakage of potassium and various enzymes, leading to reduced cellular energy and adenosine triphosphate, hypoxia, edema, and eventual necrosis and cell death. There is intense research activity to find compounds that will reduce these free radicals, since they are implicated in such a variety of diseases. However, with the possible exception of trimetazidine, an oxygen-free radical scavenger and protector[106,107] used for angina, cochliovestibular disease and retinopathy, few have yet found widespread use. Others include allopurinol, which inhibits the xanthine oxidase conversion of hypoxyxanthine to the superoxide (although this has only a weak activity in humans), superoxide dismutase or catalase (enzymes that degrade the free radicals) and α-tocopherol, an antioxidant, but these are recent innovations that have not been fully tested and have not found general use. Recently, it has been shown that indapamide and one of its major

metabolites, 5-hydroxyindapamide, possess free radical quenching activity,[108] and the effect has been compared with a known free radical scavenger α-tocopherol and a thiazide antihypertensive, trichloromethazide. Both indapamide and its metabolite were shown to quench the stable free radical 1,1-diphenyl-2-picrylhydrazyle in a concentration-dependent manner comparable to that of α-tocopherol, while trichloromethazide was found to be inactive (Fig. 8).

Similarly, indapamide, its metabolite, and α-tocopherol were able to inhibit the peroxidation of linoleic acid by the superoxide produced by hypoxanthine-xanthine oxidase, and the reduced nicotinamide-adenine dinucleotide phosphate–induced lipid peroxidation of rat liver microsomes. In another experiment using hemolysis of the human erythrocyte cell membrane by the free radical 2,2′-azobis (2-amidopropane) dihydrochloride as a measure of membrane lipid peroxidation, indapamide, at a physiologic concentration of $<10^{-5}$ mol/liter, was able to inhibit the oxidative damage to the red cell membrane. The 5-hydroxy metabolite in this experiment was slightly more active than either the parent drug or α-tocopherol, whereas trichloromethazide was again without activity in any of these experiments. Why indapamide and its metabolite should have this protective effect against free radical damage is unknown, but it does not occur with the thiazide trichloromethazide and may be a consequence of the methyl-indoline substitution of the chlorosulfonamide molecule.

Elastin and vessel rigidity: Although rarely considered as important in the pathogenesis of cardiovascular disease, elastin, a major polypeptide of connective tissue, found in most organs in the body, may play a fundamental role in atherosclerosis, reduced vascular compliance, and hypertension due to aging.[109] As one of the most unusual proteins found in nature, it is the body's natural rubber or elastomer substance and, in combination with collagen microfibrils, is associated with the continuous elastic lamella, the adventitia, sandwiched between the intima and media forming the arteries.[110] Changes in the formation and content of elastin in vascular smooth muscle and the incorporation of certain ions leads to rigidity of the vascular smooth muscle and, in addition, becomes a focus for lipid plaques. It is now well recognized that during aging, calcium and phosphate become intimately associated with elastin through neutral binding sites, forming calcium hydroxyapatite crystals that lead to calcium levels in the vasculature some 50 times higher in older patients than in younger controls.[111] In addition, during the aging processes, the relative ratio of elastin to collagen is reduced, partly because of reduced synthesis, but also because of the enhanced hydrolytic degradation of the elastin endogenous elastase.[112] This combination of events is likely to lead not only to a lack of vascular compliance and subsequent higher systolic blood pressure found in the elderly, but also to a stimulation of lipid infiltration, and subsequent atherosclerosis due to deposition of cholesterol around the apatate crystals.[113,114] It is therefore of some interest that indapamide both reduces the uptake of calcium into the cell[31] and binds preferentially to pure elastin, producing levels 40-fold higher than in buffer medium.[115] In contrast, the binding to collagen is low. This provides a rationale to explain why the drug is taken up by arterial smooth muscle and could also suggest that indapamide may positively influence the calcium-phosphate-elastin interaction. Certainly, the phosphaturic action of indapamide[37] to reduce phosphate plasma and organ levels further suggests that the drug may play a protective role against the aging development of arterial hypertension and atherosclerosis. However, more work is needed to investigate these possibilities.

Arterial compliance: As discussed previously, the vascular smooth muscle becomes more rigid and less distensible with increasing age because of the structural changes of increased media thickness and a lower elastin/collagen ratio.[116] The subsequent arterial stiffness and loss of compliance reduces the cushioning function of the ventricular pulsatile ejections leading to left ventricular hydraulic load wall stress and adverse effects on myocardial oxygen consumption. The higher pressure generated at the peak of ventricular ejection increases systolic pressure and this, rather than increased diastolic pressure, is the major risk factor in strokes, cardiac failure and other cardiovascular mortalities.[117,118] Because the viscoelastic arterial wall becomes stiffer as it is distended, the pressure-volume relationship is curvilinear and arterial compliance can only be defined for a given pressure.

Arterial compliance is therefore measured by use of propagative models of the pulse wave velocity. In an analogous fashion to changes in left ventricular hypertrophy, certain calcium antagonists and ACE inhibitors reduce pulse wave velocity in association with a reduction in blood pressure, whereas dihydralazine drugs do not, which suggests that there is a dissociation of the 2 activities. The effect of indapamide (10 mg/kg orally) on carotid artery compliance has been measured in normotensive Wistar rats and those made hypertensive by removal of 1 kidney and given deoxycorticosterone acetate-saline for 2 weeks.[119] Treatment with indapamide produced a significant improvement in carotid artery compliance in both groups compared with placebo but the effect was greater in the hypertensive (+30%) than in the normotensive rats (+18%). This difference was augmented when the rats were challenged with potassium cyanide, which removes vascular muscle tone. Thus, there remained a reserve of carotid artery compliance in normotensive rats that was not seen in the hypertensive rats. In hypertensive patients (n = 9) treated for 12 weeks, there was little change in blood flow velocity but a maximal increase occurred in volume flow (+24%), a decrease was seen in forearm vascular resistance (−28%), and an increase was seen in pulse wave velocity (+9%), but these did not reach statistical significance, possibly because of the large intersubject variability. Other studies are required to investigate these effects more fully; they have important consequences for cardiac pathology, particularly left ventricular hypertrophy.

Left ventricular hypertrophy: Hypertrophy and increased mass of the left ventricle are thought to be a consequence of high systolic blood pressure, particularly when it exceeds 180 mm Hg,[120] and a consequence of pressure distension and overload, although the exact

TABLE II Effect of Indapamide (2.5 mg) Treatment on Various Indexes of Left Ventricular Hypertrophy Measured by M-Mode Echocardiography

Reference	No. of Subjects	Treatment (weeks)	LVMI (Δ%)	LVESD (Δ%)	LVEDD (Δ%)	LVESS (Δ%)
129	14	8	−8	−6	−2	
19	9	6		−4	−6	−10*
123	9[a] young	12	−6*			
130	11[b] old	12	−14*			
14	8 Res[c]	4		−5*	−6*	−18*
	5 Non[d]	4		−3	−3	−4
131	18	52	−16*		−9	
Mean ± SD		16 ± 17	−11 ± 5	−5 ± 1	−5 ± 3	−11 ± 7

* $p < 0.05$.
[a] Mean ± SD age is 40 ± 11 years.
[b] Man ± SD age is 70 ± 7 years.
[c] Responders.
[d] Nonresponders had 23 to 40% lower drug plasma levels than responders.
LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; LVESS = left ventricular end wall stress; LVMI = left ventricular mass index; SD = standard deviation.

mechanism leading to this pathology is unknown. Whether by a direct or indirect association with hypertension, left ventricular hypertrophy is a strong predictor of sudden death with a greater incidence and severity of myocardial infarction, heart failure and cardiac rupture.[121] It could therefore be expected that all drugs that reduced blood pressure should, in principle, reduce left ventricular hypertrophy, but this does not appear to be the case. Those that do include β blockers,[122,123] ACE inhibitors,[124] methyldopa[125] and some calcium antagonists.[123] For others, like the diuretics, the effect is equivocal,[126] and with the powerful vasodilators minoxidil and hydralazine, there may be increases in left ventricular hypertrophy, despite blood pressure reductions.[126,127] This is thought to be due to an increased sympathetic tone with higher circulating levels of catecholamines.[128] Indapamide in all studies undertaken has shown a reduction in most indexes of left ventricular hypertrophy (Table II), including left ventricular mass index (−11%), left ventricular end-systolic and end-diastolic dimensions (−5%), and left ventricular end-wall stress (−11%), indicating a diminished afterload. This improvement in left ventricular hypertrophy was achieved without a deterioration in myocardial work or systolic performance as measured by the velocity of the left ventricular circumferential fiber shortening (Table II).[129,131,132] The change in left ventricular hypertrophy with indapamide, like blood pressure,[133] seems to be related to the initial levels, since there was only a 6% reduction in young subjects with an initial left ventricular mass index of 107 g/m^2 but a 14% reduction in older subjects with left ventricular mass index of 137 g/m^2. There has been some discussion as to whether drugs that reduce left ventricular hypertrophy do so by their antihypertensive activity, per se, or by some improvement in sympathetic tone.[130] Leenen et al[14] found that subjects who had a significant reduction in blood pressure also had a significant reduction in left ventricular hypertrophy, but those who had subtherapeutic drug levels had neither reduced blood pressure nor reduced left ventricular hypertrophy.

In contrast, Komajda et al[131] found an improvement in left ventricular hypertrophy for all patients after 6

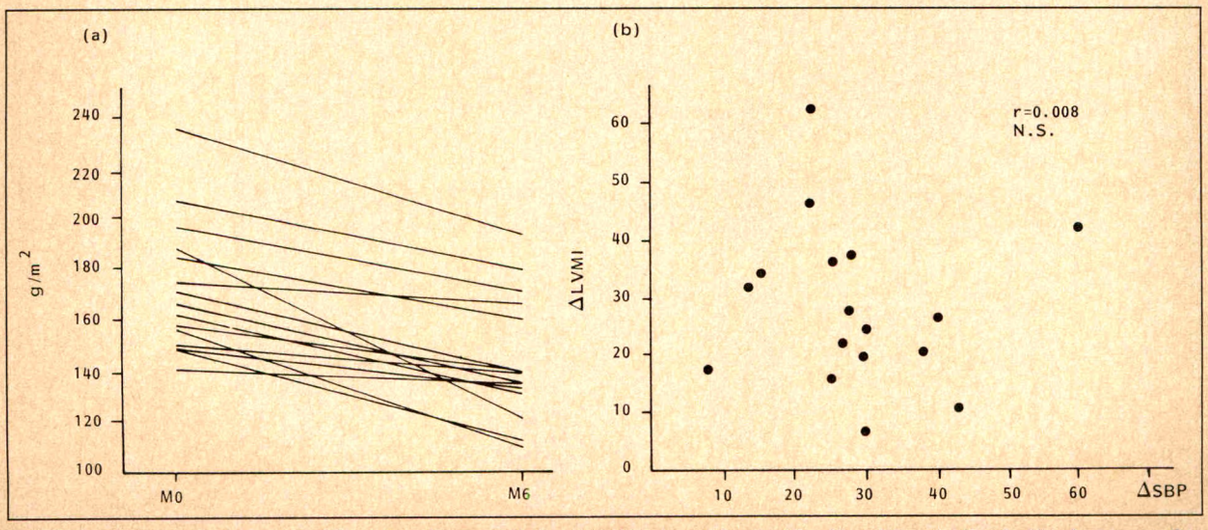


FIGURE 9. Individual changes in left ventricular mass index (LVMI) (a) and the relationship with reduction in blood pressure (b) after 6 months of treatment with indapamide, 2.5 mg.[131] M0 = month 1; M6 = month 6; N.S. = not significant; SBP = systolic blood pressure. (Modified from Grosgogeat, 1989.)

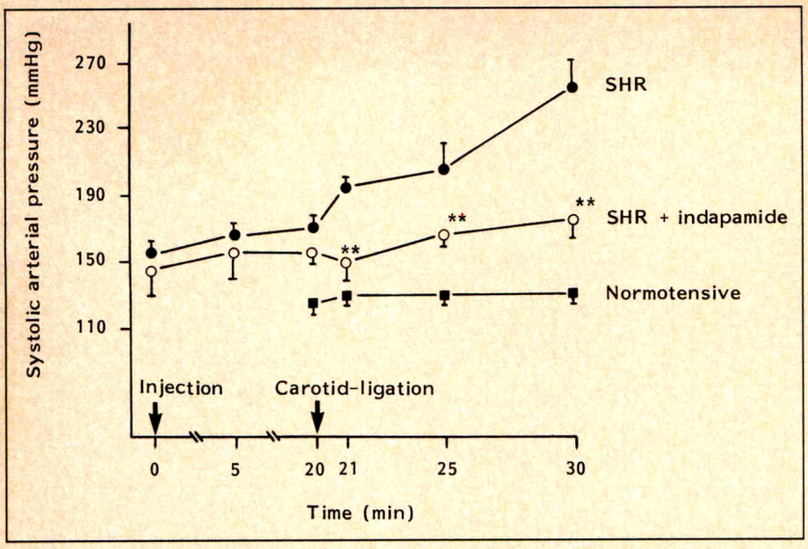


FIGURE 10. Comparison of systolic pressure in spontaneously hypertensive rats (SHR) before (*closed circles*) and after (*open circles*) indapamide (3 mg/kg, orally) and in normotensive rats (*squares*), (n = 8). **p <0.01 (significant difference from SHR before administration of indapamide).[138]

months' treatment with indapamide (Fig. 9), but this was unrelated to the decrease or final blood pressure and may be due to the variability in measuring the awake blood pressure. Other measures of blood pressure, such as diurnal systolic blood pressure or blood pressure during exercise, may be more appropriate to find a correlation with the effects on left ventricular hypertrophy.

Stroke and cerebral ischemia: Since the advent of antihypertensive therapy, the incidence of cerebral hemorrhage as a major cause of stroke is declining. Instead, minor strokes due to cerebral ischemia, which may be transient, isolated or repetitive, are occurring more frequently and are more difficult to diagnose.[134] This reduction in blood flow and supply of oxygen to the brain can be caused by thrombus formation and increases in sympathetic tone leading to vasoconstriction, which is accentuated by hypertension. Conversely, with hypotensive episodes, particularly in hypertensive patients who are too rapidly treated with antihypertensive agents, ischemia may lead to strokes due to impaired cerebral perfusion.[135] The elderly are especially at risk because the vascular smooth muscle is less compliant and unable to respond to

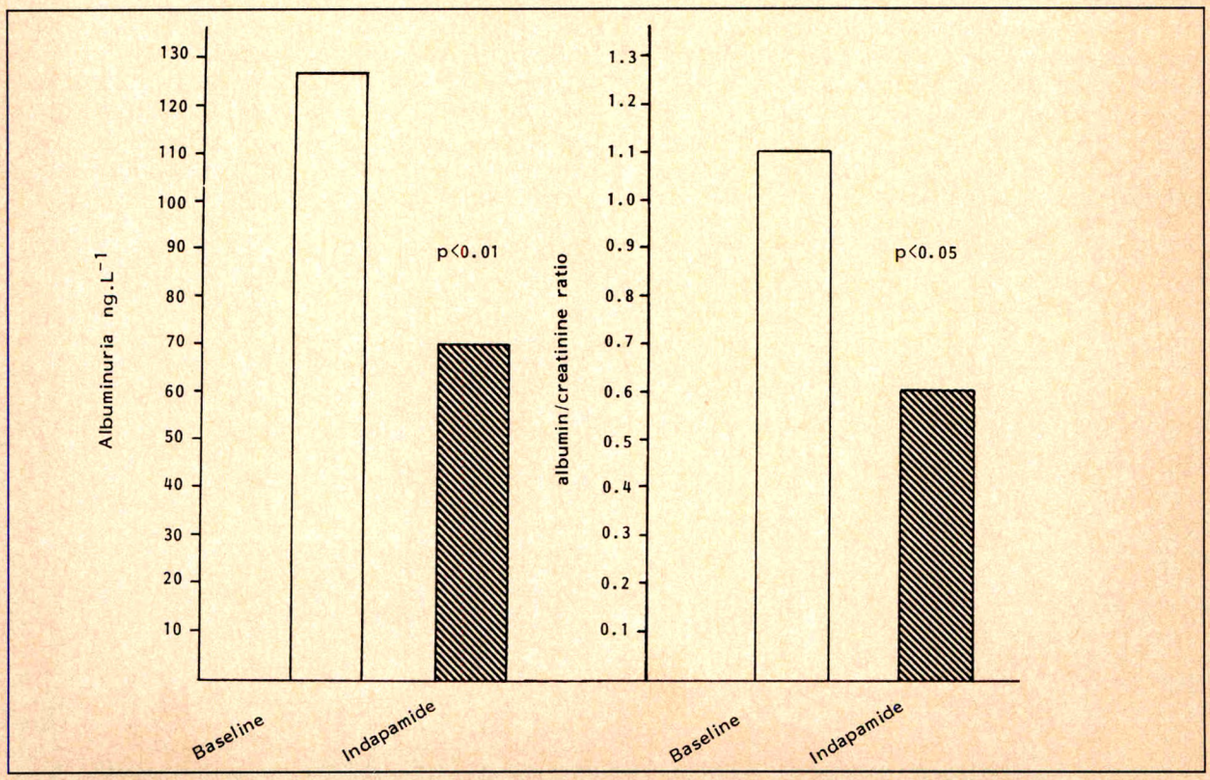


FIGURE 11. Improvement in renal function in hypertensive diabetic subjects (n = 32) treated with indapamide, 2.5 mg/day, for 2 months.[139]

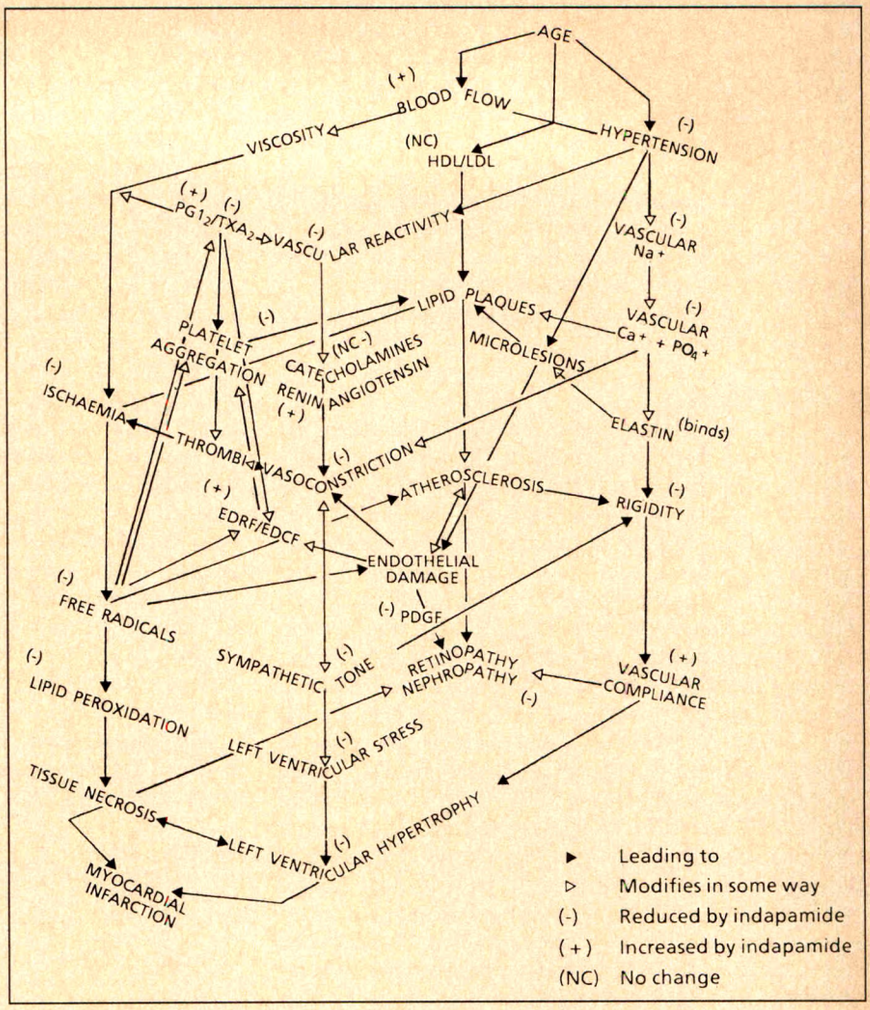


FIGURE 12. Interaction of indapamide in the pathology of the cardiovascular system. EDCF = endothelium-derived constricting factor; EDRF = endothelium-derived relaxing factor; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PDGF = platelet-derived growth factor; PGI_2 = prostacyclin; TXA_2 = thromboxane A_2.

changing blood pressure and, in addition, baroreflexes are less sensitive. From a review of published reports and their own studies, Jansen et al[135] concluded that a significant number of subjects (10%) had signs of cerebral ischemia or stroke within 2 weeks of starting antihypertensive therapy. Analysis of their results show that these patients developed symptoms within 4 days after a mean reduction from 220/125 to 146/79 mm Hg, a decrease of 36% in mean average pressure. This is equivalent to a daily reduction in blood pressure of 9 mm Hg. Strokes have rarely been reported with indapamide, and generally the drug is well tolerated in the elderly. Perhaps a reason for this is that the antihypertensive activity is gradual, taking several weeks to attain a maximal activity at a rate of change of approximately 0.3 mm Hg/day.[136] In addition, indapamide tends to "normalize" blood pressure with the degree of blood pressure reduction proportional to the initial value[133] and does not tend to decrease blood pressure below 85 mm Hg diastolic. These combined actions tend to be favorable, not only for the elderly patient prone to cerebral ischemia, but also when considering the apparent increase in myocardial ischemia noted with the "U-shaped" curve, associated with too aggressive a treatment of hypertension.[137] In addition, indapamide (3 mg/kg orally) has been shown experimentally in spontaneously hypertensive rats to significantly reduce the cerebral ischemia produced when there has been bilateral ligation of the carotid arteries (Fig. 10).[138] These workers have attributed this activity to a reduction in blood pressure without a change in heart rate and to reduction in sympathetic reactivity in these more sensitive hypertensive rats.

RENAL CONSEQUENCES OF HYPERTENSION

Another common complication of hypertension is an alteration in renal function. In the long term, hypertension might induce a certain degree of renal failure and even, in some cases, severe renal impairment, with anatomic lesions of nephroangiosclerosis. In diabetic patients, the renal involvement is more frequent, with an initial reversible microalbuminuria, developing to an irreversible macroalbuminuria. It has recently been shown that indapamide significantly reduced microalbuminuria by 45% in 32 diabetic hypertensive patients treated for 2 months (Fig. 11)[139]; this result could not be entirely explained by a reduction in systolic blood pressure, suggesting a protective effect of indapamide on renal vasculature. These results have been confirmed in a study comparing the effect of indapamide after 24 months of treatment in hypertensive type II diabetic subjects with

(n = 10) or without (n = 11) microalbuminuria.[140] In the normoalbuminuric patients, blood pressure was significantly reduced, but the albumin excretion rate, urinary IG_4 and glomerular filtration rate remained unaltered. In the microalbuminuric patients, however, there were significant reductions in blood pressure and in albumin excretion rate and IG_4 without changes in glomerular filtration rate. These findings are particularly important because albuminuria is more than an indicator of renal disease and may also be considered as an independent risk factor for widespread cardiovascular damge and mortality in diabetic patients.[141]

CONCLUSION

This review has attempted to bring together the more recent results found with indapamide, particularly with respect to the global cardiovascular risk associated with hypertension and the possible effects on all the mechanisms involved. In most instances (Fig. 12), indapamide either positively changes or at least leaves the normal physiologic protective mechanisms unaltered. Unlike the diuretics examined, indapamide stimulates the production of the vasodilator prostanoids and inhibits the synthesis of those that cause vascoconstriction. These increases in plasma prostacyclin probably lead to the enhanced EDRF activity at the endothelium and the reduction of platelet aggregation. The quenching of free radicals would also increase EDRF activity by reducing its breakdown, reduce platelet aggregation, and protect the endothelium against lipid peroxidation, particularly during reperfusion and regrowth. Because indapamide binds to elastin and inhibits calcium and phosphate uptake into the smooth muscle cell, there is the possibility that it could reduce calcium apatate deposition and therefore could reduce the incorporation of cholesterol into the vascular smooth muscle, but more studies are needed to explore this possibility.

Long-term treatment with indapamide does not alter insulin or glucose metabolism,[142] again reducing the risk of hyperglycemia reported with long-term diuretic therapy and the potential damage of the vascular system. In addition, the metabolic effects of indapamide are also characterized by the absence of deterioration of lipid metabolism, an important advantage when compared with diuretics or β blockers with no ISA.

Figure 12 attempts to interrelate some of the many known factors that participate in the progression of cardiovascular disease. Although the macrodeterminants of cholesterol and hypertension are well defined, to what degree each of the microeffects influences the whole system is unknown. In recent years, factors from platelets and endothelium have been found to be involved and science will continue to find more. However, although they may affect only a relatively small part of the whole, they should not be dismissed as unimportant. In aging, perhaps at the start of the disease, only one small part may be perturbed and, like the "butterfly effect" in deterministic chaos, this progressively changes the balance of the system over time until turbulence occurs, manifesting itself as a pathologic event. It is for this reason that drugs that are used in the treatment of cardiovascular disease should be investigated in all systems to show at least that there is no change and, at most, that they are improved.

The results from a number of large-scale studies show that antihypertensive therapy reduces blood pressure and reduces the incidence of strokes but has little effect on coronary artery disease, myocardial infarction and death. However, these studies used a minimum of antihypertensive drugs and at sometimes inappropriate doses. In addition, some of these agents have been demonstrated to have some deleterious effects on associated cardiovascular risk factors, such as lipid profile, glucose metabolism or left ventricular hypertrophy, so that the cardiovascular benefit that might have been expected from blood pressure control was blunted by other unwanted effects. In contrast, animal and clinical studies show that indapamide does not deteriorate and may actually improve many of the cardiovascular risk factors, an interesting potential for long-term use in hypertensive patients. Certainly, a therapeutic agent like indapamide, with its ease of use, its widespread acceptance over many years, and its cardioprotective potential described here, needs to be investigated further to see if it can fulfill these expectations as an ideal inexpensive treatment.

Acknowledgment: We thank Julia Chatten for her perseverance, patience and pictorial skills undertaken in the preparation of this review.

REFERENCES

1. Caruso FS, Szabadi RR, Wukovich RA. Pharmacokinetics and clinical pharmacology of indapamide. *Am Heart J 1983;106:212–220.*

2. Campbell DB. Indapamide. A diuretic or vasoactive antihypertensive? *Drugs Today 1984;20:suppl 1:1–7.*

3. Chaffman M, Heel RC, Brogden RN, Speight TM, Avery GS. Indapamide. A review of its pharmacodynamic properties and therapeutic efficacy in hypertension. *Drugs 1984;28:189–235.*

4. Campbell DB. The possible mode of action of indapamide: a review. *Curr Med Res Opin 1983;8:suppl 3:9–24.*

5. Moore RA, Seki T, Ohsumi S, Oheim K, Kyncl J. Desnoyers P. Antihypertensive action of indapamide and review of pharmacology and toxicology. *Curr Med Res Opin 1977;5:suppl 1:25–32.*

6. Borkowski KR, Hicks PE, Moore RA. The effects of indapamide on the responses of electrical stimulation of in vitro preparations from the rat. *Br J Pharmacol 1981;72:172P–173P.*

7. Miyazaki M, Morishita S, Toda N. Vasodilator effect of indapamide in dog mesenteric vasculature. *Jpn J Pharmacol 1985;39:402–405.*

8. Usui H, Kanda M, Ohsumi S, Seki T, Toda N. Effects of indapamide, a new non-thiazide anti-hypertensive diuretic agent, on smooth muscles of blood vessels. *Folia Pharmacol Jpn (Nippon Yahurigahu Zasshi) 1978;74:389–396.*

9. Finch L, Hicks PE, Moore RA. Changes in vascular reactivity in experimental hypertensive animals following treatment with indapamide. *J Pharm Pharmacol 1977;29:739–743.*

10. Hicks PE. The effects of long term oral treatment with indapamide on the development of DOCA-salt hypertension in rats: vascular reactivity studies. *Clin Exp Hypertens 1979;1:713–731.*

11. Weidmann P, Beretta-Piccoli C, Meier A, Grimm M, Keusch G, Gluck Z. Effects of short-term norepinephrine infusion on plasma catecholamines, renin and aldosterone in normal and antihypertensive man. *Hypertension 1980;2:623–630.*

12. Grimm M, Weidmann P, Meier A, Keusch G, Ziegler W, Gluck Z, Beretta-Piccoli C. Correction of altered noradrenaline reactivity in essential hypertension by indapamide. *Br Heart J 1981;46:404–409.*

13. Noveck RJ, Quiroz A, Giles T, Ryan JR, McMahon RG, Solomon TA, Rothman J, Caruso FS, Vukovich RA. Hemodynamic effects on a new antihypertensive-diuretic, indapamide, in healthy male volunteers. *Clin Pharmacol Ther 1982;31:257.*

14. Leenen FHH, Smith DL, Farkas RM, Boer WH, Reeves RA, Marquez Julio A. Cardiovascular effects on indapamide in hypertensive patients with or without renal failure. A dose-response curve. *Am J Med 1988;84:suppl 1B:76–85.*

15. Carretta R, Fabris B, Bardelli M, Muiesan S, Bellini G, Bianchetti A, Campanacci L. Resting systemic haemodynamics after chronic treatment of essential hypertension with indapamide. In: Ogilvie RI, Safar M eds. Indapamide and the current Treatment of Hypertension. New Prospects in Hypertension. *London: John Libbey Eurotext, 1986:27–31.*
16. Acchiardo SR, Skoutakis VA. Clinical efficacy, safety, and pharmacokinetics of indapamide in renal impairment. *Am Heart J 1983;106:237–244.*
17. Canicave JCI, Lesbre FX. Measurement of peripheral resistance by carotid pulse wave recordings: study of a vasopressor and an antihypertensive agent. *Curr Med Res Opin 1977;5:suppl 1:79–82.*
18. Velasco M, Urbina-Quintana A, Hernandez-Pieretti O. Cardiovascular haemodymamic effects of indapamide and atenolol in hypertensive patients. *Curr Ther Res 1982;31:1007–1017.*
19. Gensini G, Esente P, Giambartolomei A. A systemic haemodynamic evaluation of indapamide. *Clin Ther 1983;5:475–482.*
20. Ogilvie RI, Langlois S, Kreeft J. Indapamide versus hydrochlorothiazide in essential hypertension: measurement of peripheral resistance using plethysmography (abstr). *Curr Med Res Opin 1983;8:suppl 3:67.*
21. Villarreal H, Nunez-Poissot E, Anguas MC, Degandarias L, Meza U. Effects of the acute and chronic administration of indapamide on systemic and renal haemodynamics in essential hypertension. *Curr Med Res Opin 1983;8:suppl 3:135–139.*
22. Magrini F, Buzzetti G, De Giovanni F, Cerati D, Macchi G, Mondadori C. Systemic and pulmonary hemodynamic effects of indapamide in patients with mild arterial hypertension. *J Cardiovasc Pharmacol 1985;7:281–285.*
23. Burgess CD, McKee CEL, Wilson CA, Warren DJ. The effect of indapamide on muscle blood flow in hypertensive patients. *Postgrad Med J 1981;57:suppl 2:23–25.*
24. Novo S, Licata G, Pinto A, Dari G, Fazio M, La Menza B, Immordino R, Strano A. Effects of indapamide on systemic haemodynamics and on arterial flow of the calf in patients with essential hypertension. *Folio Angiologica 1981; 29:221–225.*
25. Carretta R, Fabris B, Tonutti L, Bellini G, Battilana G, Bianchetti A, Campanacci L. Effect of indapamide on the baroreceptor reflex in essential hypertension. *Eur J Clin Pharmacol 1983;24:579–584.*
26. Ferrara LA, Rubba P, Iannuzzi A, Fasano ML. Haemodynamic changes in peripheral arterial circulation during antihypertensive treatment with captopril, methyldopa and indapamide. *Int J Clin Pharm Res 1984;4:389–393.*
27. Mironneau J, Gargouil YM. Action of indapamide on excitation-contraction coupling in vascular smooth muscle. *Eur J Pharmacol 1979;57:56–67.*
28. Mironneau J, Savineau JP, Mironneau C. Compared effects of indapamide, hydrochlorothiazide and chlorthalidone on electrical and mechanical activities in vascular smooth muscle. *Eur J Pharmacol 1981;75:109–113.*
29. Mironneau J, Savineau JP, Mironneau C. Effect of indapamide on the electromechanical properties of rat myometrium and rat portal vein. *J Pharmacol Exp Ther 1986;236:519–525.*
30. Schleiffer R, Ketz J, Gairard A. L'indapamide modifie les échanges de ^{45}Ca après angiotensine au niveau de l'aorte isolée de rat. *J Pharmacol 1980;3:342.*
31. Mironneau J, Mironneau C. Indapamide and vascular smooth muscle cells. A review. *JAMA (SE Asia) 1988;suppl 4:31–33.*
32. Ljunghall S, Hedstrand H. Serum phosphate is inversely related to blood pressure. *Br Med J 1977;1:553–554.*
33. Gruchow HW, Sobocinski KA, Baroriak JJ. Alcohol, nutrient intake and hypertension in US adults. *JAMA 1985;253:1567–1570.*
34. Binders RJM, Geersten JAM, Van Os CH. Increased transport of inorganic phosphate in renal brush borders of spontaneous hypertensive rats. *Am J Physiol 1986;250:F470–F475.*
35. Saglikes R, Massry SG, Iseki K, Brunton LL, Buxton ILO, Vlachakis N, Campese VM. Effect of phosphate depletion on blood pressure and vascular reactivity to norepinephrine and angiotensin II in the rat. *Am J Physiol 1985;248:F93–F99.*
36. Plante GE, Lafreniere MC, Sirois P. Effect of indapamide on phosphate metabolism and vascular reactivity. *Miner Electrolyte Metab 1985;11:336.*
37. Plante GE, Lafreniere MC, Pham Thi Tam, Sirois P. Effect of indapamide on phosphate metabolism and vascular reactivity. *Am J Med 1988;84:suppl 1B:26–30.*
38. Plante GE, Dessurault P. Hypertension in elderly patients: a comparative study of indapamide and hydrochlorothiazide. In: Ogilvie RI, Safar M eds. Indapamide and the current treatment of hypertension. New prospects in hypertension. *London: John Libbey Eurotext, 1986:41–49.*
39. Campbell DB, Phillips EM. Short term effects and urinary excretion of the new diuretic, indapamide in normal subjects. *Eur J Clin Pharmacol 1974;7:407–414.*
40. Bloch R, Steimer C, Welsch M, Schwartz J. L'effet hypocalciurique de l'hydrochlorothiazide de la chlorthalidone, de l'indapamide et de l'acide tiènilique. *Thèrapie 1981;36:567–574.*
41. Waal-Manning HJ, Doesburg RMN. Randomised crossover trial of indapamide and conventional diuretics in hypertension: metabolic and renal effects (abstr). *NZ Med J 1982;95:19–20.*
42. Leary WP, Reyes AJ. Diuretics, magnesium, potassium and sodium. *S Afr Med J 1982;61:279–280.*
43. Porter GA. The role of diuretics in the treatment of heart failure. *JAMA 1980;244:1614–1616.*
44. Reyes AJ, Leary WP, Van der Byl K. Urinary magnesium output after a single dose of indapamide in healthy adults. *S Afr Med J 1983;64:820–822.*
45. Spannbrucker N, Achhammer I, Metz P, Glocke M. Comparative study on the antihypertensive efficacy of torasemide and indapamide in patients with essential hypertension. *Arzneimittelforschung 1988;38:190–193.*
46. Lake CR, Ziegler MG, Coleman MD, Kopin IJ. Hydrochlorothiazide induced sympathetic hyperactivity in hypertensive patients. *Clin Pharm Ther 1979;26:428.*
47. Schiffl H, Weidmann P, Meir A, Ziegler WH. Relationship between plasma catecholamines and urinary catecholamine excretion rates in normal subjects and diseased states. *Klin Wochenschr 1981;3(59):837–844.*
48. Leenen FHH, Smith DL, Moer WH, Marquez-Julio A. Diuretic and cardiovascular effects of indapamide in hypertensive subjects: a dose-response curve. *Cur Med Res Opin 1983;8:suppl 3:47–52.*
49. De Oritz H, De Quattro E, Stephanian E, De Quattro V. Long-term effectiveness of indapamide in hypertension: neural, renin and metabolic responses. *Clin Exp Hypertens 1983;5:665–672.*
50. Noveck RJ, McMahon FG, Quiros A, Giles T. Extrarenal contributions to indapamide's antihypertensive mechanism of action. *Am Heart J 1983;106:221–229.*
51. Chalmers JP, Wing LMH, Grygiel JJ, West MJ, Graham JR, Bune AJ. Effects of once daily indapamide and pindolol on blood pressure, plasma aldosterone concentration and plasma renin activity in a general practice setting. *Eur J Clin Pharmacol 1982;22:191–196.*
52. Lebel M, Grosse JH, Belleau LJ, Langlois S. Antihypertensive effect of indapamide with special emphasis on renal prostaglandin production. *Curr Med Res Opin 1983;8:suppl 3:81–86.*
53. Furchgott RF, Zawadski JV. The obligatory role of endothelial cells in the relaxation of the arterial smooth muscle by acetylcholine. *Nature 1980;288:373–376.*
54. Vanhoutte PM, Luscher TF. Vascular endothelium and hypertension. *J Cardiovasc Pharmacol 1987;10:suppl 4:19–24.*
55. Vanhoutte PM, Luscher TF. Role of the endothelium in the pathophysiology of hypertension. *JAMA (SE Asia) 1988;4:suppl 4:34–42.*
56. Miller VM, Vanhoutte PM. Endothelial dependent responses in isolated blood vessels of lower vertebrates. *Blood Vessels 1986;23:225–235.*
57. Vanhoutte PM. The end of the quest. *Nature 1987;327:459–460.*
58. Gryglewski RJ, Palmer RMJ, Moncada S. Superoxide is involved in the breakdown of endothelial derived relaxing factor. *Nature 1986;320:454–456.*
59. Palmer RMJ, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelial derived relaxing factor. *Nature 1987;327:524–526.*
60. Collins SP, Griffith TM, Henderson AH, Lewis MJ. Endothelial derived relaxing factor alters calcium fluxes in rabbit aorta: cyclic guanosine monophosphate mediated effect. *J Physiol (Lond) 1986;381:427–437.*
61. Schini VB, Dewey J, Vanhoutte PM. Effects of indapamide on endothelium-dependent relaxations in isolated canine femoral arteries. *Am J Cardiol 1990; 65:6H-10H.*
62. Editorial 1987. EDRF. *Lancet 1987;2:137–138.*
63. Collier J, Vallance P. Endothelium derived relaxing factor is an endogenous vasodilator in man. *Br J Pharmacol 1989;97:639–641.*
64. Kish B. Electron microscopy of the atrium of the heart. 1. Guinea pig. *Exp Med Surg 1956;14:99–112.*
65. Jamieson JD, Palade GE. Specific granules in atrial muscle cells. *J Cell Biol 1964;23:151–172.*
66. De Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extracts in rats. *Life Sci 1981;28:89–94.*
67. Thibault G, Garcia R, Cantin M, Genest J. Purification of three atrial natriuretic factors and their amino acid composition. *Hypertension 1983;5:75–80.*
68. Flynn TG, De Bold ML, De Bold AJ. The amino acid sequence of an atrial peptide with potent diuretic and natriuretic properties. *Biochem Biophys Res Commun 1983;117:859–865.*
69. Seidan NG, Lazure C, Chretien M, Thibault G, Garcia R, Cantin M, Genest J, Nutt RF, Brady SF, Lyle TA. Amino acid sequence of an atrial peptide with potent diuretic and natriuretic properties. *Proc Natl Acad Sci USA 1984;81: 2640–2644.*
70. Zivin RA, Condra JH, Dixon AF, Seidah NG, Chretien M, Nemer M, Chamberland M, Drouin J. Molecular cloning and characterization of DNA sequences encoding rat and human atrial natriuretic factors. *Proc Natl Acad Sci USA 1984;81:6325–6329.*
71. Laragh JH. Atrial natriuretic hormone, the renin-aldosterone axis, and blood pressure-electrolyte homeostasis. *N Engl J Med 1985;313:1330–1340.*
72. Nakaoka H, Imataka K, Amano M, Fujii J, Ishibashi M, Yamaji T. Plasma levels of atrial natriuretic factors in patients with congestive heart failure. *N Engl J Med 1985;313:892–893.*
73. Oliver JR, Twidale N, Lakin C, Cain M, Tonkin AM. Plasma atrial natriuretic polypeptide during and after reversion of paroxysmal supraventricular tachyarrhythmias. *Br Heart J 1988;59:458–462.*

74. Gerzer R, Witzgall H, Tremblay J, Gutkowska J, Hamet P. Rapid increase in plasma and urinary cyclic GMP after bolus injection of atrial natriuretic factor in man. *J Clin Endocrinol Met 1985;61:1217.*
75. Matsuoka H, Hirata Y, Ishii M, Sugimoto T. Atrial natriuretic polypeptide in normal and hypertensive states. *JAMA (SE Asia) 1988;4:suppl:43–46.*
76. Cusson JR, Thibault G, Kuchel O, Hamet P, Cantin M, Larochelle P. Cardiovascular, renal and endocrine responses to low doses of atrial natriuretic factor in mild essential hypertension. *J Human Hypertens 1989;3:89–96.*
77. Huxley VH, Tucker VL, Verburg KM, Freeman RH. Increased capillary hydraulic conductivity induced by atrial natriuretic peptide. *Circ Res 1987; 60:304–307.*
78. Ogura T, Mitsui T, Yamamoto I, Katayama E, Ota Z, Ogawa N. Effect of indapamide on atrial natriuretic polypeptide receptor in spontaneously hypertensive rat kidney. *Res Commun Chem Phathol Pharmacol 1986;54:291–298.*
79. Levy RI. Changing perspectives in the prevention of coronary heart disease. *Am J Cardiol 1986;57:17G–26G.*
80. Kannel WB. Status of risk factors and their consideration in antihypertensive therapy. *Am J Cardiol 1987;59:80A–90A.*
81. Gbeassor FM, Grose JH, Lebel M. Influence of diuretics on prostaglandin and thromboxane synthesis. *Clin Invest Med 1982;5(2–3):26B.*
82. Grose JH, Gbeassor FM, Lebel M. Differential effects of diurectics on eicosanoid biosynthesis. *Prostaglandins, Leukotrienes Med 1986;24,2–3:103–109.*
83. Izumi Y, Honda M, Hatano M. Antihypertensive mechanism of indapamide. *Jpn Pharmacol Ther 1986;14:9–15(6049–6055).*
84. Honda M, Izumi Y, Hatano M. Blood pressure lowering action of indapamide. Effect on urine 6-keto-prostaglandin Fl alpha. *Pharm Rev (Kusuri no Chishiki) 1987;38:3–7.*
85. Soma M, Manku MS, Jenkins DK, Horrobin PV. Prostaglandins and thromboxane outflow from the perfused mesenteric vascular bed in spontaneously hypertensive rats. *Prostaglandins 1982;29:323–333.*
86. Numabe A, Uehara Y, Hirawa N, Takada S, Yaki S. Effects of thiazide diuretic on vascular eicosanoid system of spontaneously hypertensive rats. *J Hypertens 1989;7:493–499.*
87. Lebel M, Gbeassor FM, Grose JH. Effet antihypertenseur de l'indapamide et action sur la biosynthèse des métabolites de l'acide arachidonique. *JAMA (Edition Française) 1984;9:suppl 88:21–23.*
88. Smith MC, Dunn MJ. The role of prostaglandins in human hypertension. *Am J Kidney Dis 1985;5:A32.*
89. Dorian B, Larrue JM, DeFeudis FV, Salari H, Borgeat P, Braquet P. Activation of prostacyclin synthesis in cultured aortic smooth muscles by diuretic antihypertensive drugs. *Biochem Pharmacol 1984;33:2265–2269.*
90. Biggs R. Platelet lipid interactions in atherosclerosis. *Thromb Haemost 1978;39:253–254.*
91. Vlachakis ND, Aledort L. Platelet aggregation in relation to plasma catecholamines in patients with hypertension. *Atherosclerosis 1979;32:451–460.*
92. Hamet P, Skuherska R, Pang S, Tremblay J. Abnormalities of platelet function in hypertension and diabetes. *Hypertension 1985;7:135–142.*
93. Shirahase H, Suzuki Y, Kunitomo K, Osumi K, Kakeya S. Inhibitory effect of indapamide (Natrix) on platelet aggregation in vitro. *J Med Pharm Sci (Igaku To Yakugaku) 1985;14:1614–1618.*
94. Shirahase H, Suzuki Y, Kunitomo K, Osumi S, Kaketani N. Platelet aggregation inhibition of indapamide (Natrix) in vitro-2. *J Med Pharm Sci (Igaku to Yakugaku) 1987;18:1021–1024.*
95. Morishita S, Wada K, Osumi S, Kaketani N. Effect of indapamide (Natrix) on perfusing pressure in extirpated mesenteric blood vessel. *J Med Pharm Sci (Igaku to Yakugaku) 1987;18:1017–1020.*
96. Uehara Y, Nagata T, Ishimitsu T, Matsouoka H. Free radical scavenging effects of indapamide on prostacyclin generation in vascular smooth muscle cells of rats. *Am Hypertens Assoc. in press.*
97. Salvemini D, De Nucci G, Sneddon JM, Vane JR. Superoxide anions enhance platelet adhesion and aggregation. *Br J Pharmacol 1989;97:1145–1150.*
98. Hamet P. Platelets and vascular smooth muscle cells in hypertension. *Drugs Today, in press.*
99. Hamet P, Chouinard S, Nehme D, Hadrava V, Russo CR. Effect of antihypertensive therapy on growth potential on platelets in hypertension and diabetes (abstr). *IV European Meeting on Hypertension, Milan 1989; 336.*
100. Carretta R, Fabris B, Fischetti F, Muiesan S, Bardelli M, Melchior C, Cesanelli R, Pizzolitto A, Giraldi T, Lo Greco P, Campanacci L. Platelet alpha 2-adrenoceptor modifications induced by long-term treatment with indapamide in essential hypertension. *Am J Med 1988;84:suppl 1B:31–35.*
101. Van Bummelen P. The relevance of intrinsic sympathomimetic activity for beta blocker induced changes in plasma lipids. *Cardiovasc Pharmacol 1983; 5:suppl 1:51–55.*
102. Louis WJ, Howes LG, Krum H, McNeil JJ. Metabolic risks and hypertension. *JAMA (SE Asia) 1988;4:suppl 4:13–20.*
103. Weidmann P, Bianchetti MG, Mordasini R. Effects of indapamide and various diuretics alone or combined with beta-blockers on serum lipoproteins. *Curr Med Res Opin 1983;8:suppl 3:123–134.*
104. Cardona R, Lopez B, Fragachan F. Effects of indapamide on the lipid profile of patients with essential hypertension. In: Ogilvie RI, Safar M, eds. Indapamide and the Current Treatment of Hypertension. New Prospects in Hypertension. *London: John Libbey Eurotext, 1986:93–97.*
105. Gotzen R, Meyer-Sabellek W, Heitz J, Arntz HR, Schulte KL. Plasma lipids and lipoproteins during long-term antihypertensive treatment with indapamide. In: Ogilvie RI, Safar M, eds. Indapamide and the Current Treatment of Hypertension. New Prospects in Hypertension. *London: John Libbey Eurotext, 1986:99–103.*
106. Maridonneau-Parini I, Harpey C. Effect on trimetazidine on membrane damage induced by oxygen free radicals in human red cells. *Br J Clin Pharmacol 1985;20:148–151.*
107. Deroux A. La Trimètazidine (Vastarel 20 mg), caractéristiques cliniques générales dans le traitement des maladies ischémiques du coeur à partir d'une revue des principales études cliniques. *Concours Med 1987;109:suppl 36:3493–3497.*
108. Tamura A, Sato T, Fujii T. Quenching action of oxygen radical by indapamide and its metabolites. *J Med Pharm Sci (Igaku to Yakugaku) 1987;18:1469–1473.*
109. Ito H. Age related alteration of aortic elastin and effects of hypertension in SHRSP. *Acta Med Kinki Univ 1979;4:403–414.*
110. Sandberg LB, Soskel NT, Leslie JG. Elastin structure, biosynthesis, and relation to disease states. *N Engl J Med 1981;304:566–579.*
111. Yu SY, Blumenthal HT. The calcification of elastic tissue. In: Wagner BM, Smith DE, eds. The Connective Tissue. *Baltimore: Williams & Wilkins, 1967:17–49.*
112. Ito H, Kwan C-Y, Suzuki T, Daniel EE. Vascular elastase-like activities in rats—relation to hypertension. *J Hypertens 1986;4:suppl 3:S97–S99.*
113. Urry DW. Neutral sites for calcium ion binding to elastin and collagen: a charge neutralization theory for calcification and its relationship to atherosclerosis. *Proc Natl Acad Sci USA 1971;68:810–814.*
114. Yu SY. Calcification processes in atherosclerosis. *Adv Exp Med Biol 1974;43:403–423.*
115. Nicholls P. Uptake of 14C-indapamide by rat tissues: an in vitro study (abstr). *Br Pharmacol Soc, Bristol, April 1989;*
116. Safar ME, London GM. Arterial and venous compliance in sustained essential hypertension. *Hypertension 1987;10:133–139.*
117. Kannel WB, Wolf PA, McGee DL, Dawber TR, McNamara P, Castelli WP. Systolic blood pressure, arterial rigidity and risk of stroke. The Framingham Study. *JAMA 1981;245:1225–1229.*
118. Rutan GH, Kuller LH, Neaton JD, Wentworth DN, McDonald RH, McFate-Smith W. Mortality associated with diastolic hypertension and isolated systolic hypertension among men screened for multiple risk. Factor Intervention Trial. *Circulation 1988;77:504–514.*
119. Levy BI, Poitevin P, Safar ME. Effects of indapamide on the mechanical properties of the arterial wall in deoxycorticosterone acetate-salt hypertensive rats. *Am J Cardiol 1990;65:28H–32H.*
120. Kannel WB, Gordon T, Olfit D. Left ventricular hypertrophy by ECG. Prevalence, incidence and mortality in the Framingham study. *Ann Intern Med 1969;71:89–106.*
121. Marcus ML, Harrison DG, Chilian WM. Alterations in the coronary circulation in hypertrophied ventricles. *Circulation 1987;75:suppl:19–25.*
122. Trimarco B, Ricciardelli B, De Luca N, Volpe M, Veniero A, Cuoccolo A. Effect of acebutols on ventricular haemodynamics and anatomy in systemic hypertension. *Am J Cardiol 1984;53:791–796.*
123. Mace PJE, Littler WA, Glover DR, Rowlands DB, Stallard TJ. Regression of left ventricular hypertrophy in hypertension: comparative effects of three different drugs. *J Cardiovasc Pharmacol 1985;7:suppl 2:s52–55.*
124. Nakashima Y, Fouad FM, Tarazi RC. Regression of left ventricular hypertrophy from systemic hypertension by enalapril. *Am J Cardiol 1984;53:1044–1049.*
125. Fouad FM, Nakashima Y, Tarazi RC, Salcedo E. Reversal of left ventricular hypertrophy in hypertensive patients treated with methyldopa. *Am J Cardiol 1982;49:795–801.*
126. Drayer JIM, Gardin JM, Weber MA, Aronow WS. Cardiac muscle mass during vasodilation therapy of hypertension. *Clin Pharmacol Ther 1983;33:727–732.*
127. Sen S, Tarazi RC, Khairallah RP, Bumpus FM. Cardiac hypertrophy in spontaneously hypertensive rats. *Circ Res 1974;35:775–781.*
128. Tarazi RC, Sen S. Catecholamines and cardiac hypertrophy. In: Catecholamines and the heart. Royal Society of Medicine International Congress and Symposium Series, No 8. *London. Academic Press, 1979;57–67.*
129. Dunn FG, Hillis WS, Tweddel A, Rai AP, Lorimer AR. Non-invasive cardiovascular assessment of indapamide in patients with essential hypertension. *Postgrad Med J 1981;57:suppl 2:19–22.*
130. Rowlands DB, Glover DR, Ireland MA, McLeay RAB, Stallard TJ, Watson RDS, Littler WA. Assessment of left-ventricular mass and its response to antihypertensive treatment. *Lancet 1982;1:467–470.*
131. Komajda M, Klimczak K, Boutin B, Brackman F, Guez D, Grosgogeat Y. Effects of indapamide on left ventricular mass and function in systemic hypertension with left ventricular hypertrophy. *Am J Cardiol 1990;65;37H–42H.*
132. Horgan JH, O'Donovan A, Teo KK. Echocardiographic evaluation of left ventricular function in patients showing an antihypertensive and biochemical

response to indapamide. *Postgrad Med J 1981;57:suppl 2:39–41.*
133. Campbell DB, Lowe S, Taylor D, Turner P, Walsh N. A fresh approach to the evaluation of antihypertensive agents. *Hypertension 1985;7:suppl 2:143–151.*
134. Haberman S, Capildeo R, Rose FC. The changing mortality of cardiovascular disease. *Q J Med 1978;47:71–88.*
135. Jansen PAF, Schulte BPM, Meyboom RHB, Gribnau FWJ. Antihypertensive treatment as a possible cause of stroke in the elderly. *Age Ageing 1986;15:129–138.*
136. Turner P, Volans GN, Rogers HJ. A preliminary controlled evaluation on the antihypertensive effects of indapamide. *Curr Med Res Opin 1977;4:596–601.*
137. Cruickshank JM, Thorp JM, Zachanas FM. Benefits and potential harm of lowering high blood pressure. *Lancet 1987;1:581–584.*
138. Delbarre B, Delbarre G. The effect of indapamide on an experimental model of cerebral ischemia in hypertensive rats. *Am J Med 1988;54:suppl 1B:20–25.*
139. Janka HV. Hypertension and microalbuminuria in diabetic patients on indapamide. *Abstract from IV European Meeting on Hypertension, Milan 1989;391.*
140. Gambardella S, Frontoni S, Felici MG, Gatta R, Scoppola A, Spallone V. Efficacy and tolerance of indapamide in normoalbuminuric and microalbuminuric type II diabetic patients (abstr). Proceedings from Antihypertensive Strategy for the 90's: from Pathology to Patients Well-being, *Barcelona, April 1989.*
141. Deckert T, Felot-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoedenevoldsen A. Albuminuria reflects widespread vascular damage. The Steno hypothesis. *Diabetologia 1989;32:219–226.*
142. Harrower ADB, McFarlance G, Donnelly T, Gray CE. Effect on indapamide on blood pressure and glucose tolerance in non-insulin-dependent diabetes. *Hypertension 1985;7:suppl II:161–163.*

Effects of Indapamide on the Mechanical Properties of the Arterial Wall in Deoxycorticosterone Acetate-Salt Hypertensive Rats

Bernard I. Levy, MD, PhD, Pierre Poitevin, and Michel E. Safar, MD

An experimental model of "in situ" isolated carotid artery has been used to evaluate the static mechanical properties of the arterial wall in 12-week-old Wistar and deoxycorticosterone acetate (DOCA)-salt hypertensive rats. The rats were made hypertensive by left kidney removal, DOCA (50 mg) tablet implantation for 2 weeks, and saline diet (NaCl 9‰ solution as beverage). Normotensive control rats (n = 24) and DOCA-salt hypertensive rats (n = 24) received indapamide, 10 mg/kg, or placebo by gavage 12 hours and 1 hour before measurements were obtained. The rats were anesthetized (pentobarbital 50 mg/kg), intubated and ventilated, and a midsternal thoracotomy was performed. A first catheter was introduced into the ascending aorta through the right carotid artery. A perivascular ultrasonic flow probe was placed around the ascending aorta and allowing simultaneous recording of the phasic ascending aortic pressure and flow. Systolic and diastolic pressure, cardiac output and heart rate were directly measured. Peripheral resistance and systemic arterial compliance were calculated from hemodynamic records. After hemodynamic measurements, a segment of the left carotid artery was then isolated in vivo and its volume-pressure relationship was recorded before and 30 minutes after total abolition of the vascular muscle tone by local incubation with a potassium cyanide solution (KCN) (100 mg/liter) for pressures ranging from 50 to 175 mm Hg. The carotid compliance (CC) (μl/mm Hg) was calculated, for every pressure step, as the slope of the volume-pressure curves.

Indapamide significantly reduced the arterial pressure in hypertensive rats, and this was related to a marked decrease in total peripheral resistance. Heart rate was not modified by indapamide. In contrast, systemic arterial compliance was significantly increased by treatment with indapamide in the hypertensive group.

Furthermore, there were significant differences in CC (mean ± standard error of the mean) measured in Wistar and DOCA-salt animals. Maximal values of CC measured for pressure values close to the operating pressures in both groups were higher in the untreated DOCA-salt group than in the normotensive Wistar group (0.17 ± 0.02 and 0.14 ± 0.01 μl/mm Hg, respectively, $p < 0.001$). Maximal values of CC were increased by 32 and 30% after KCN poisoning in Wistar and DOCA-salt rats, respectively ($p < 0.01$). The treatment by indapamide induced a significant increase in CC both in the normotensive and hypertensive groups (+18 and +30%, respectively, $p < 0.01$). Although there was a reserve of CC in Wistar rats pretreated with indapamide (significant decrease in stiffness after KCN poisoning), there was no further increase in CC in hypertensive rats when KCN poisoning was performed after treatment with indapamide.

These results suggest that (1) in the first weeks of hypertension induced by DOCA and salt diet, a significant decrease occurred in arterial stiffness possibly related to modifications in vascular connective tissues and in arterial vascular smooth muscle tone; and (2) acute treatment with indapamide induced an increase in arterial compliance in both normotensive and hypertensive rats.

(Am J Cardiol 1990;65:28H–32H)

From the Institut National de la Santé et de la Recherche Médicale, Unité 141, Hôpital Lariboisière, and the Centre de Recherche sur l'hypertension artérielle, Hôpital Broussais, Paris, France.

Address for reprints: Bernard Levy, INSERM U141, Hôpital Lariboisière, 75010 Paris, France.

Chronic arterial hypertension is characterized by major alterations in the structural and functional properties of the arterial walls.[1–3] The main processes involved are hypertrophy and hyperplasia of the smooth muscle, resulting in thickening of the media, and alterations of the proteins of the extracellular matrix.[4,5] Both processes are responsible for stiffening the wall of the aorta and large arteries.[6,7]

The mechanical properties of the wall of the aorta and the large arteries are one of the components of the afterload faced by the left ventricle and thus one of the determinants of the pressure-flow relationship in the arterial system.[8,9] A decrease in arterial compliance results in an increase in systolic and a decrease in diastolic blood pressures,[10–12] both changes that may be deleterious to the heart. Increased systolic pressure forms an extra load during cardiac ejection and decreased diastolic blood pressure may diminish the myocardial perfusion.

Indapamide has diuretic and antihypertensive effects which have been known for a long time.[13] One of the possible mechanisms of its antihypertensive action is an effect on the vascular tone and reactivity in resistance vessels.[14–16] The aim of this work was to investigate the effects of indapamide on the mechanical properties of the large compliant arteries in deoxycorticosterone acetate (DOCA)-salt hypertensive rats.

METHODS

The experiments were performed in 12-week-old Wistar rats. Under pentobarbital anesthesia, 24 rats were rendered hypertensive by left kidney removal, DOCA tablet (50 mg) implantation and saline diet for 2 weeks (NaCl 9‰ solution as beverage). The same number of rats (n = 24) were sham-operated and received standard diet during the same period. Normotensive and DOCA-salt hypertensive rats were then randomized to receive either indapamide, 10 mg/kg, or placebo orally 12 hours and 1 hour before hemodynamic measurements were obtained.

Hemodynamic study: The rats were anesthetized with intraperitoneal pentobarbital (50 mg/kg) and a constant body temperature was kept by a thermostated operating table. After induction of anesthesia, the trachea was cannulated and connected to a rodent respirator (model 680, Harvard apparatus, South Natick, Massachusetts). A midsternal throacotomy was performed, and then the ascending aorta and the root of the left carotid artery were exposed. Arterial blood pressure was first recorded through a right carotid catheter connected to a P231D pressure transducer (Statham, Gould, Cleveland, Ohio). A perivascular ultrasonic flow probe was placed around the ascending aorta and connected to a range-gated 20-MHz device. The simultaneous ascending aortic pressure and flow were then recorded. The systemic arterial compliance was estimated from phasic pressure and flow using a simple resistance-compliance model of the systemic arterial compartment.[17]

Mechanical study[18,19]: The upper end of the left carotid artery was catheterized with an 80-cm-long nylon tube (internal diameter 0.6 mm), filled with a solution of Tyrode with albumin (4%) and Evans blue (0.03%). The tube was connected to a manometer pressurized at adjustable pressure levels. A 3-way tap was connected between the manometer and the nylon tube, permitting a part of the tube to be filled in order to observe the position of the meniscus. The root of the left carotid artery was dissected and a removable clamp was positioned at the junction of the aortic arch and the carotid artery. This preparation allowed exclusion, in situ, of 18 to 20 mm of nonexposed carotid artery (Fig. 1).

To start the measurements, the segment of isolated artery was submitted to atmospheric pressure for 5 minutes and the position of the meniscus was noted. The artery was then submitted to a pressure step of 50 mm Hg. The movement of the meniscus, representing changes in the contained volume within the artery, was followed and noted every 10 seconds for 5 minutes. These

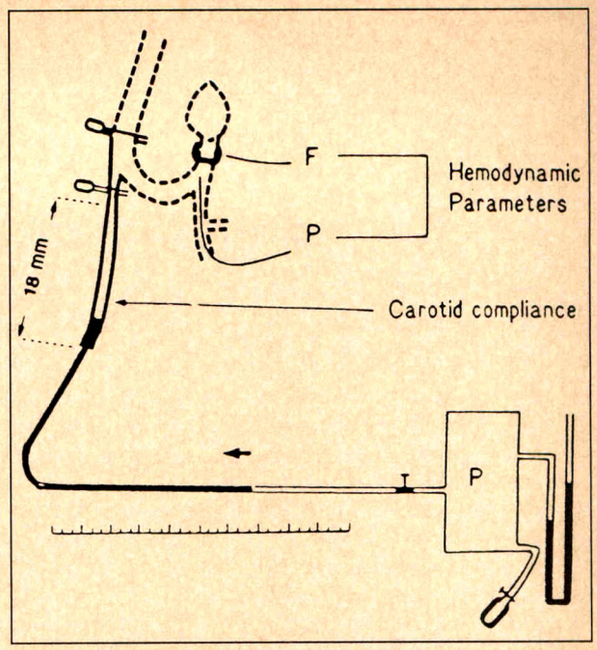


FIGURE 1. Representation of the experimental hemodynamic system. F = flow; P = pressure.

measurements were repeated for pressures ranging from 50 to 175 mm Hg by steps of 25 mm Hg. The static compliance of the isolated segment of artery (i.e., carotid compliance [CC] μl/mm Hg) was calculated for each

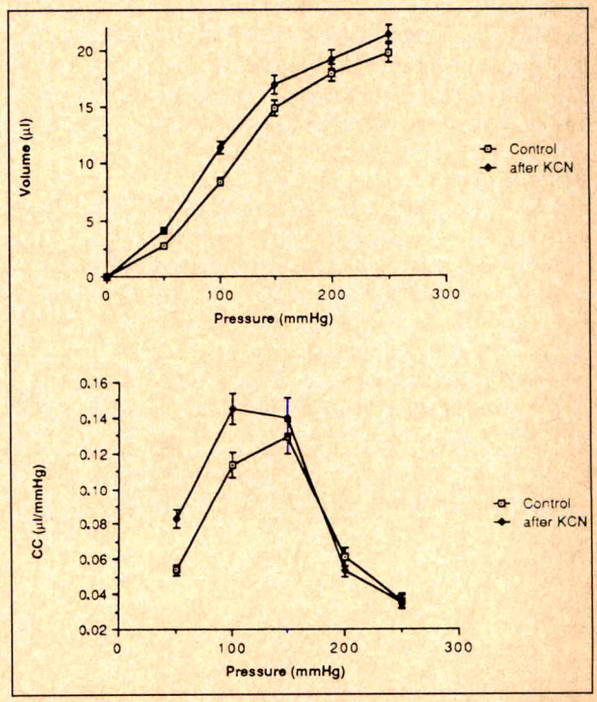


FIGURE 2. *Top*, carotid volume pressure curve recorded in untreated Wistar rats in control conditions and after poisoning of the smooth muscle by potassium cyanide (KCN). *Bottom*, carotid compliance (CC) vs transmural pressure obtained by derivation from the upper curves.

TABLE I Hemodynamic Results (Mean ± SD) Obtained in Control Normotensive Rats and in Untreated and Treated (Indapamide 10 mg/kg) DOCA-Salt Hypertensive Rats (n = 12 for Each Group)

	SBP (mm Hg)	DBP (mm Hg)	CO (ml/min)	HR (beats/min)	TPR (mm Hg/ml/s)	SAC (10^{-3}ml/mm Hg)
1. Normotensive	114	90	42	340	130	4.12
2. Placebo	15	17	7	35	32	0.83
3. Hypertensive	146	106	58	310	121	3.94
Placebo	14	18	13	42	47	0.99
Hypertensive	110	72	68	296	75	5.12
Treated	26	26	15	22	42	1.22
Statistical significance						
1 vs 2	p <0.01	p <0.01	p <0.05	NS	NS	NS
1 vs 3	NS	NS	p <0.01	NS	p <0.05	p <0.05
2 vs 3	p <0.05	p <0.01	NS	NS	p <0.05	p <0.05

CO = cardiac output; DBP = diastolic blood pressure; HR = heart rate; NS = not significant; SAC = systemic arterial compliance; SBP = systolic blood pressure; SD = standard deviation; TPR = total peripheral resistance.

level of pressure as the quotient of the volume increase and the pressure step imposed (25 mm Hg) (Fig. 2).

The clamp on the carotid excluding the root of the left carotid artery was then removed and the artery was washed and filled with a saline solution of potassium cyanide (KCN, 100 mg/liter). The KCN solution was maintained in the carotid artery for 30 minutes, a period sufficient to poison the vascular smooth muscle.[20] After isolating the same segment of carotid as used previously by clamping the root again, the measurement of the pressure-volume relationship was performed in the KCN-treated vessel.

Statistical analysis: Results are expressed as mean ± 1 standard deviation. A 2-way analysis of variance with repeated measurements was used to test differences related to experimental models or treatment and interaction, or a combination. Differences between groups were evaluated using the Newman-Keuls test.[21]

RESULTS

Table I summarizes the hemodynamic results obtained in normotensive and hypertensive rats.

Untreated normotensive versus deoxycorticosterone acetate-salt hypertensive rats: The hypertensive rats had significantly higher cardiac output than the normotensive control rats. In contrast, there were no significant differences between the peripheral reistance and the systemic arterial compliance calculated in untreated hypertensive and normotensive rats. Figure 3 shows the CC values measured between 50 and 175 mm Hg in the 4 groups. Table II shows the CC values for a given pressure step in different groups and conditions. For the whole pressure range, CC was significantly higher in the untreated hypertensive group than in the normotensive control group ($p < 0.05$). Similarly, after KCN poisoning, CC was higher in the untreated hypertensive group ($p < 0.05$).

Effects of indapamide: Gavage with indapamide induced a significant decrease in systolic and diastolic arterial pressure in DOCA-salt hypertensive rats. Cardiac output was not significantly increased by indapamide, and peripheral resistances were markedly reduced. The systemic arterial compliance was significantly increased by treatment in the hypertensive group. Similarly, both in normotensive and hypertensive rats, CC was significantly increased after treatment with indapamide ($p < 0.05$ and $p < 0.01$, respectively, Table II).

TABLE II Values of Carotid Compliance (CC) for the 100 to 125 mm Hg Perfusion Pressure Step in Control and After KCN Conditions

	CC(μl/mm Hg) for 100 to 125 mm Hg Pressure	
	Control	After KCN
Normotensive	0.137	0.180
Placebo	0.047 *	NS 0.041
Normotensive	0.161	0.187
Treated	0.036	0.040
Hypertensive	0.145 *	0.192 *
Placebo	0.056 †	0.063 †
Hypertensive	0.212	0.242
Treated	0.062	0.048

* $p < 0.05$; † $p < 0.01$
KCN = potassium cyanide; NS = not significant.

COMMENTS

DOCA-salt hypertension is a characteristic model in which the initial alteration is volume overload. Consequently, an increase in cardiac output is expected, as observed in the pressure study together with the significant increase in blood pressure.

The main finding of the present study was the increase in CC observed in the untreated DOCA-salt hypertensive rats at each given value of blood pressure compared with that in the normotensive Wistar rats, indicating an active response of the hypertensive arterial wall. The increase in compliance despite a significant increase in systemic pressure is difficult to explain. An increase in total vascular compliance after a volume overload could be a compensatory mechanism partially limiting the increase in the heart-filling pressure. Increased arterial compliance could also be a compensatory mechanism at this early phase of hypertension. This has been evidenced by Cox[22] in the same experimental model and related to a decrease

in the collagen content of the arterial media. Cox suggested that during the early stage of hypertension, the wall stress to which the smooth muscle cells are subjected is increased. This could promote a modification of the rate of synthesis or degradation of arterial wall connective tissue elements in such a fashion that the ratio of collagen to elastin decreases, resulting in an increased compliance. Our results in CC after KCN poisoning of the smooth muscle, and thus no more active tension in the media of the carotid artery, confirm this interpretation. This response of the arterial wall would represent an attempt by the smooth muscle to maintain some hemodynamic or mechanical variable constant despite the increase in mean arterial pressure. Such a response would represent a form of structural autoregulation.

Whereas the increase in compliance in DOCA-salt hypertensive rats affected only the carotid artery and not the systemic circulation, a significant increase in both systemic and CC was observed after administration of indapamide. The increase in CC was observed at any given value of transmural pressure, indicating that the compliance enhancement was drug induced and not pressure induced. The increase in arterial compliance was associated with a significant decrease in peripheral resistances, indicating that drug-induced changes were located in both the small and large arteries. Similar results have been observed in humans with a reset of the brachial artery-blood pressure relationship, indicating drug-induced changes in the arterial wall.[23]

Prostacyclin (PGI_2), a product of arachidonic acid metabolism,[24–27] is one of the determinants of local vascular smooth muscle tone. In a recent work, Izumi et al[28] showed that indapamide induces changes in PGI_2 production in spontaneously hypertensive rats. The relaxing effect on the vascular smooth muscle produced by indapamide could be mediated by changes in PGI_2 production.

In conclusion, our results suggest that (1) in the first weeks of hypertension induced by DOCA and salt diet, a significant decrease occurred in arterial stiffness, possibly related to modifications in vascular connective tissues and in arterial vascular smooth muscle tone; (2) acute treatment with indapamide induced an increase in arterial compliance both in normotensive and hypertensive rats, associated with a significant antihypertensive effect; and (3) the relaxing effect on the arterial smooth muscle could be mediated by local changes in PGI_2 production.

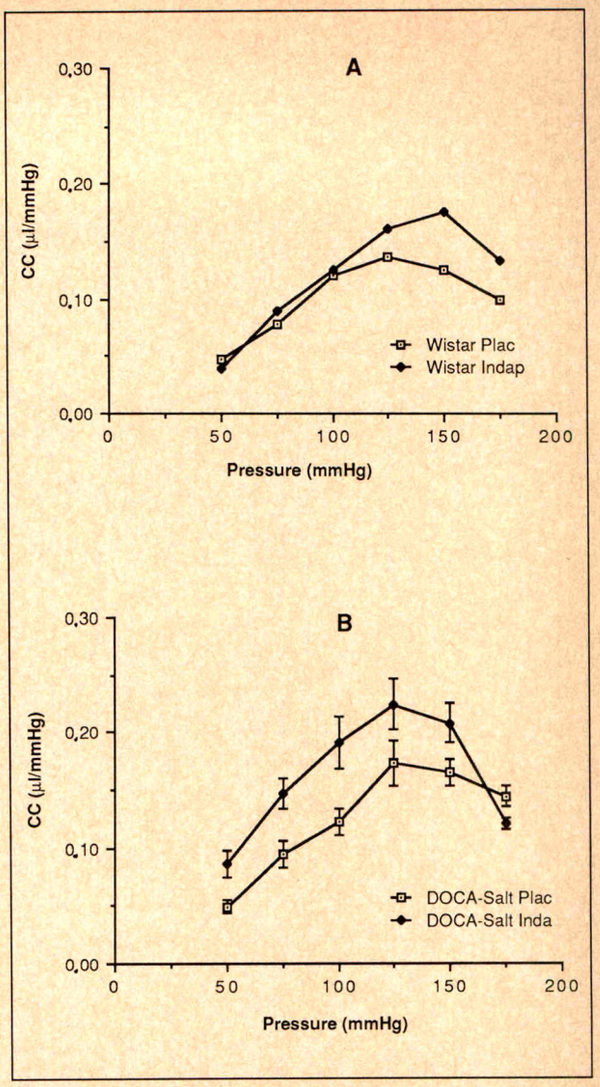


FIGURE 3. *A*, carotid compliance (CC) in untreated and treated normotensive rats; *B*, carotid compliance in untreated and treated deoxycorticosterone acetate (DOCA)-salt hypertensive rats. Inda = indapamide; Plac = placebo.

REFERENCES

1. Ferrone RA, Walsh GM, Tsuchiya M, Frohlich ED. Comparison of hemodynamics in conscious spontaneous and renal hypertensive rats. *Am J Physiol 1979;236:H403–H408.*

2. Folkow B. Physiological aspects of primary hypertension. *Physiol Rev 1982;62:347–504.*

3. Frohlich ED. Hemodynamics of hypertension. In: Genest J, Koiw E, Kuchel O, eds. Hypertension: Physiopathology and Treatment. *New York: McGraw-Hill, 1977;45–49.*

4. Olivetti G, Anversa P, Melissari M, Loud AV. Morphometry of medial hypertrophy in the rat thoracic aorta. *Lab Invest 1980;42:559–565.*

5. Wiener J, Loud AV, Giacomelli F, Anversa P. Morphometric analysis of hypertension induced hypertrophy of rat thoracic aorta. *Am J Pathol 1980;88: 619–634.*

6. Cox RH. Comparison of arterial mechanics in normotensive and spontaneously hypertensive rats. *Am J Physiol 1979;237:159–167.*

7. Simon AC, Safar ME, Levenson JA, London GM, Levy BI, Chau NP. An evaluation of large arteries compliance in man. *Am J Physiol 1979;237:550–554.*

8. O'Rourke MF. Arterial function in health and disease. *New York: Churchill Livingstone, 1982;276.*

9. Milnor WR. Hemodynamics. *Baltimore: Williams & Wilkins, 1982;157–197.*

10. Elzinga G, Westerhof N. Pressures and flow generated by the left ventricle against different impedances. *Circ Res 1973;32:178–186.*

11. Randall OS, Van Den Bos GC, Westerhof N. Systemic compliance, does it play a role in the genesis of essential hypertension? *Cardiovasc Res 1984;18:455–462.*

12. Babalis D, Levy B, Azancot I, Masquet C, Beaufils P. Ventricular function and arterial mechanical characteristics in patients with congestive cardiomyopathy. *Int J Cardiol 1984;5:361–364.*

13. Kyncl J, Oheim K, Seki T, Solles A. Antihypertensive effect of indapamide in various experimental models. *Arzneimittelforschung 1975;25:1491–1495.*

14. Myazaki M, Morishita S, Toda N. Vascular effect of indapamide in dog resistance vessels. *Jpn J Pharmacol 1985;39:402–405.*

15. Finch L, Hicks PE, Moore RA. The effects of indapamide on vascular reactivity in experimental hypertension. *Curr Med Res Opin 1977;5:44–54.*

16. Osumi S. Mechanism of antyhypertensive action of indapamide. Effect on vascular response. *Acta Schol Med Univ Gifu 1982;30:627–649.*

17. Benessiano J, Levy BI, Michel JB. Instantaneous aortic blood flow measurement with range-gated Döppler flowmeter in anesthetized rat. *J Pharmacol Methods 1985;14:99–110.*
18. Levy BI, Benessiano J, Poitevin P, Lukin L, Safar ME. Systemic arterial compliance in normotensive and hypertensive rats. *J Cardiovasc Pharmacol 1985;7:S28–S32.*
19. Levy BI, Michel JB, Salzmann JL, Azizi M, Poitevin P, Safar ME, Camilleri JP. Effects of chronic inhibition of converting enzyme on mechanical and structural properties of arteries in rat renovascular hypertension. *Circ Res 1988;63:227–239.*
20. Dobrin PB, Rovick AA. Influence of vascular smooth muscle on contractile mechanics and elasticity of arteries. *Am J Physiol 1969;217:1644–1651.*
21. Zar JH. Biostatistical Analysis. *Englewood Cliffs NJ: Prentice Hall, 1984.*
22. Cox RH. Alterations in active and passive mechanics of rat carotid artery with experimental hypertension. *Am J Physiol 1979;237:H597–H605.*
23. Safar ME, Laurent St, Safavian A, Pannier B, Asmar R. Sodium and large arteries in hypertension. *Am J Med 1988;84:suppl:15B–19B.*
24. Gryglewski RJ, Botting RM, Vane JR. Mediators produced by endothelial cell. *Hypertension 1988;12:530–548.*
25. Moncada S, Gryglewski R, Bunting S, Vane JR. An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. *Nature 1976;263:663–665.*
26. Buchanan MR, Haas TA, Lagarde M, Guichardant M. 13-hydroxyoctadecadienoic acid is the vessel wall chemorepellent factor (LOX). *J Biol Chem 1985;260:16056–16059.*
27. Hopkins NK, Oglesby TD, Bundy GW, Gorman RR. Biosynthesis and metabolism of 15-hydroxyperoxy5,8,11,13-eicosatetraenoic acid by human umbilical vein endothelial cells. *J Biol Chem 1984;259:14048–14058.*
28. Izumi Y, Honda M, Hatano M. Antihypertensive mechanism of indapamide in spontaneously hypertensive rats. *Jpn Pharmacol Ther 1986;14:6048–6054.*

Cardiovascular Effects of Antihypertensive Drugs — Involvement in the Therapeutic Choice

Manuel Luque-Otero, MD, and Carmen Fernandez-Pinilla, MD

Hypertensive patients are at an increased risk of developing cerebrovascular and cardiovascular disease. Treatment has resulted in a substantial reduction in cerebrovascular deaths but not in cardiovascular mortality. As the number of deaths from myocardial infarction exceeds the sum of all other hypertension-related mortalities, these results are disappointing. The hypothesis that metabolic side effects of many antihypertensive drugs offset the potential benefit of decreasing blood pressure is of particular interest. In established hypertension there is an increase in total peripheral resistance. Long-term therapy with diuretics decreases vascular resistance. This is also evident with dihydropyridine calcium antagonists, vasodilators, angiotensin-converting enzyme inhibitors and α blockers. In patients with hypertension, an increased wall to lumen ratio occurs in resistance vessels where mechanisms such as smooth muscle hypertrophy and increased amounts of elastin and collagen are present. In small resistance vessels, long-term antihypertensive therapy has a positive effect, but the effect in large arteries is variable.

(Am J Cardiol 1990;65:33H–36H)

From the Hypertension Unit, Hospital Universitario San Carlos, Complutense University, Madrid, Spain.

Address for reprints: M. Luque-Otero, MD, Hypertension Unit, Hospital Universitario San Carlos, Complutense University, Madrid, Spain.

Cardiovascular disease remains the leading cause of death in the industrialized world. During the last 20 years, several epidemiologic studies have identified risk factors for this disease: arterial hypertension, hyperlipidemia, diabetes mellitus, cigarette smoking, and an increased dietary intake of saturated fats.[1] The association of 2 or more of these risk factors results in a synergistic rather than an additive effect on a patient's cardiovascular risk. Essential hypertension has long been associated with an increased occurrence of cardiovascular disease. Both cerebral hemorrhage and cerebral infarction are very strongly correlated with the level of blood pressure. In the Framingham study, borderline hypertensives (patients with blood pressure between 140/90 and 160/95 mm Hg) exhibited a morbidity ratio for stroke of 85 per 1,000 patient years, and those with pressure greater than 160/95 mm Hg had a ratio of 207 per 1,000 patient years, whereas normotensives with a blood pressure of less than 140/90 mm Hg had a morbidity ratio of 45 per 1,000 patient years. Thus, hypertensive patients had a 4 to 6 times higher incidence of stroke than did normotensive subjects.[2] Similar results have been found for coronary artery disease, the risk being 2 to 2.5 times higher in hypertensive patients than in normotensive controls.[1]

Active treatment of hypertension as a preventive measure has proved effective. However, the beneficial effects have been mainly due to a reduction in cardiovascular complications other than coronary artery disease. Cerebrovascular disease has the most consistent response to blood pressure reduction. The placebo-controlled trials of antihypertensive therapy, mainly using diuretics or β blockers as first-line drug treatment, have shown that such therapy reduces the incidence of stroke by an average of 45%.[3] This percentage of reduction was greater (67%) in the earlier trials such as the Veterans Administration trials,[4] which included patients with the highest pretreatment blood pressures. The reduction in the number of strokes was approximately of the magnitude expected from the reduction of blood pressure, suggesting that the risk of stroke is reversible with treatment. In contrast, antihypertensive therapy appears to have less effect on morbidity caused by coronary artery disease than on cerebrovascular complications.[5] Most trials of antihypertensive therapy have generally shown either no change or small reductions in the incidence of myocardial infarction, in contrast with the expected reduction of 25 to 30% derived from the magnitude of reduction in blood pressure and the slope of the relationship between blood pressure and risk of myocardial infarction.[6] As the number of deaths from myocardial infarction alone exceeds

the sum of all other hypertension-related deaths, these results are disappointing. However, several studies have come close to showing a beneficial effect of antihypertensive treatment on coronary artery disease as well.

The study of Berglund et al[7] suggested that treatment of hypertensive patients with β blockers could reduce morbidity and mortality from coronary artery disease. The results of the International Prospective Primary Prevention Study (IPPPSH), a randomized double-blind trial of men and women aged 40 to 64 years, with uncomplicated essential hypertension and a diastolic blood pressure between 100 and 125 mm Hg treated with placebo or the β-blocker oxprenolol, indicate how the expected benefit of the active treatment was present only in nonsmoking men who had half the cardiac event rate (5.4 per 1,000 patient years). In contrast, sudden deaths, myocardial infarctions and cerebrovascular event rates were not significantly different despite the lower blood pressure in the group treated with oxprenolol.[8]

In the Medical Research Council (MRC) study,[3] more than 17,000 essential hypertensive patients were randomized to treatment with bendrofluazide, propranolol or placebo. The coronary event rate was not significantly lower in the β-blocker group (4.8 per 1,000 patient years) compared either with the bendrofluazide (5.6 per 1,000 patient years) or placebo groups (5.5 per 1,000 patient years). The difference in the incidence of fatal and nonfatal myocardial infarction between placebo and treatment groups was a nonsignificant 7%. As in the IPPPSH study,[8] the coronary event rate in nonsmoking men was less with propranolol (5 per 1,000 patient years) than with either bendrofluazide (7.4 per 1,000 patient years) or placebo (7.5 per 1,000 patient years). In the MAPHY Study,[9] 3,234 patients were randomized to treatment with metoprolol or thiazide diuretics. Total mortality was significantly lower for patients taking metoprolol than for those taking thiazide diuretics because of fewer deaths from stroke (2 vs 9, $p = 0.043$) and coronary artery disease (36 vs 43, $p = 0.048$). In contrast with the MRC and the IPPPSH trials, total mortality was significantly lower in both smokers (13.2 per 1,000 patient years) and nonsmokers (5.7 per 1,000 patient years) treated with metoprolol than in those treated with a diuretic (19.7 and 6.3 per 1,000 patient years, respectively). This could be related to the cardioselectivity of metoprolol. Smoking induces an increase in epinephrine[10] which, in smokers receiving nonselective β blockade with propranolol or oxprenolol, might lead to an α-receptor-mediated constriction in peripheral resistance vessels.

In summary, a review of all the data from the numerous hypertension trials has not revealed consistent findings between the relationship of treatment and the reduction in the incidence of coronary events. Although the cause of this phenomenon remains unknown, several explanations have been offered. The hypothesis that the metabolic side effects of thiazide diuretics and β blockers may diminish the benefits of blood pressure reduction, especially in patients with mild hypertension, is of particular interest.[11] Thiazide diuretics reduce serum potassium and increase the frequency of ventricular ectopic beats.[12] In addition, several studies have shown an increase in plasma total cholesterol and triglyceride levels and an increase in low-density lipoprotein (LDL) cholesterol levels during diuretic treatment.[11,13] Thiazides also impair carbohydrate tolerance, especially when administered in high doses,[14] and hyperglycemia is another risk predictor for coronary artery disease. Thus, it seems reasonable that while the level of blood pressure is reduced, an increase in the level of other risk factors such as plasma lipids and plasma glucose offsets the initial benefit achieved.

Indapamide, a thiazide-like diuretic, is a potent antihypertensive drug with minimal diuretic activity and does not have the deleterious metabolic effects of other diuretics. Indapamide does not significantly modify serum lipids[15] and does not appear to have the same effect on serum potassium levels as thiazides. Moreover, indapamide does not impair glucose tolerance,[16] even in the diabetic patient.[17] Indapamide should be considered as an alternative to thiazide treatment, especially in hypertensive diabetic patients.

Treatment with most β blockers is associated with an increase in serum triglyceride levels. The effect of these drugs on cholesterol levels differs among the various β blockers. Nonselective β blockers without intrinsic sympathomimetic activity (ISA) tend to reduce high-density lipoprotein (HDL) cholesterol levels. Selective β blockers without ISA decrease HDL cholesterol and in some studies increase total cholesterol levels. Nonselective β blockers with ISA induce more discrete changes in triglycerides with an increase in HDL cholesterol, particularly during treatment with pindolol.[18] Even if it is not known whether a drug-induced increase in cholesterol levels can increase coronary artery disease risk, it has been demonstrated that increased serum concentrations of total and LDL cholesterol correlate with the probability of developing coronary artery disease.[19]

In contrast with diuretics and β blockers, angiotensin-converting enzyme inhibitors and calcium antagonists do not alter the serum lipid profile.[20,21] $Alpha_1$ blockers do not cause adverse lipid changes but decrease total and LDL cholesterol and increase HDL cholesterol.[22] Unfortunately, despite this favorable effect on risk factors, there are no trials on the effect of these newer antihypertensive drugs on cardiovascular morbidity and mortality associated with high blood pressure.

HEMODYNAMIC EFFECTS OF ANTIHYPERTENSIVE DRUGS

The main hemodynamic finding in established hypertension is an elevated systemic vascular resistance with normal cardiac output at rest.[23] Children in the highest percentiles of the blood pressure distribution exhibit the reverse; cardiac output is elevated and total peripheral resistance is normal.[24] In the elderly hypertensive patient, however, cardiac output may be depressed and systemic vascular resistance greatly increased.[25] In summary, except during the early phase of hypertension and perhaps in young patients with uncomplicated hypertension, an increase in total peripheral resistance is the hemodynam-

ic hallmark of virtually all forms of clinical hypertension at any stage of the disease.

Thus, it seems reasonable to treat hypertension with drugs that interfere with vasoconstrictor mechanisms which decrease vascular resistance. Most of the antihypertensive drugs appear to have such an effect on resistance vessels.[26] During the early phase of the administration of diuretics, volume depletion occurs, resulting in a decrease in cardiac output and a reflex increase of systemic vascular resistance. However, long-term administration of diuretics is associated with a reduction in total peripheral resistance.[27] Indapamide, a thiazide-like diuretic that possesses vasodilatory and diuretic properties, decreases blood pressure by reducing the vascular resistance.[28]

Beta blockers, especially those without ISA, initially reduce cardiac output by exerting negative chronotropic and inotropic effects on the heart. Despite an adjustment of vascular resistance during long-term treatment with these drugs, vascular resistance will remain elevated, often above pretreatment values.[29] Calcium antagonists, particularly dihydropyridine derivatives, reduce total peripheral resistance, and this may cause a mild increase in heart rate. Converting enzyme inhibitors and α blockers have no effect on heart rate and they decrease blood pressure through a reduction in systemic vascular resistance.

EFFECTS OF HIGH BLOOD PRESSURE ON RESISTANCE VESSELS

Most studies of patients in the established phase of hypertension have demonstrated structurally changed resistance vessels with an increased wall to lumen ratio[30] due to several factors such as smooth muscle hypertrophy and increased amounts of elastin and collagen tissue.[30,31] In the large peripheral arteries, several studies have shown that arterial distensibility is reduced in patients with hypertension when compared with age- and sex-matched controls.[32,33] Arterial compliance is also reduced in patients with hypertension. This reduction is observed for the same mean arterial pressure as that of controls, therefore reflecting abnormalities in the intrinsic properties of the arterial wall.[34]

The regression of the structural vascular abnormalities in hypertensive patients is difficult to demonstrate. Hypertension in human subjects is usually not detected and is treated only when the hypertensive state has lasted for several years; thus, it is reasonable to assume that most hypertensive patients had adaptive vascular changes that were only partially reversible. Using a hemodynamic approach based on the plethysmographic assessment of resistance during maximal vasodilatation obtained by a combination of arterial occlusion, muscle exercise and direct and indirect heating, Sivertsson and Hansson[35] found that in the vasculature of the hand, long-term antihypertensive therapy has a positive effect. Complete normalization of the vascular structural abnormalities could not be demonstrated. In the vasculature of the leg no regression of vascular changes has been demonstrated. This may be due to man's erect posture, which exposes the vessels in the legs to higher pressures. In the forearm vasculature, regression of vascular changes was observed with pindolol, a β blocker with ISA, but not with metoprolol, a β blocker devoid of ISA,[36] suggesting that pindolol during periods of low sympathetic tone may act as a β_2 agonist,[37] thus causing vasodilatation.

The effect of antihypertensive drugs in large arteries is quite different. According to Safar,[38] for a given decrease in blood pressure, the caliber of large arteries may be unchanged (α and β blockers, indapamide), decreased (dihydralazine) or increased (calcium antagonists and converting enzyme inhibitors). Similar results have been reported for compliance. Alpha- and β-blocking drugs and dihydralazine did not modify the compliance, whereas calcium antagonists and converting enzyme inhibitors increased the compliance. Arterial compliance is reduced in hypertension and a possible improvement in the functional capacity of large arteries may be extremely important with possible consequences in cardiac performance and vascular damage.

REFERENCES

1. Kannel WB, Stokes J. Hypertension as a cardiovascular risk factor. In: Bulpitt CJ, ed. Handbook of Hypertension. vol 6. Epidemiology of Hypertension. *New York: Elsevier, 1985;15–34.*

2. Kannel WB, Wolf PA, Verter J, McNamara PM. Epidemiologic assessment of the role of blood pressure in stroke. The Framingham Study. *JAMA 1970;214: 301–310.*

3. Medical Research Council Working Party. MRC trial of treatment of mild hypertension. *Br Med J 1985;291:97–104.*

4. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effect of treatment of morbidity in hypertension. Results in patients with diastolic blood pressure averaging 115 through 129 mm Hg. *JAMA 1967;202: 1028–1034.*

5. Moser M. A decade of progress in the management of hypertension. *Hypertension 1983;5:808–813.*

6. Dollery CT. Risk predictors, risk indicators and benefit factors in hypertension. *Am J Med 1987;82:1A:2–8.*

7. Berglund G, Sannersted R, Andersson O, Wedel H, Wilhelmsen L, Hansson L, Sivertsson R, Wikstrand J. Coronary heart disease after treatment for hypertension. *Lancet 1978;1:1–5.*

8. The IPPPSH Collaborative Group. Cardiovascular risk and risk factors in a randomized trial of treatment based on the beta-blocker oxprenolol: The International Prospective Primary Prevention Study in Hypertension (IPPPSH). *J Hypertens 1985;3:379–392.*

9. Wikstrand J, Warnold I, Olsson G, Tuomilehto J, Elmfeldt D, Berglund G. Primary prevention with metoprolol in patients with hypertension. Mortality results from the MAPHY study. *JAMA 1988;259:1976–1982.*

10. Cryer PE, Haymond MW, Santiago JW, Shah SD. Norepinephrine and epinephrine release and adrenergic medication of smoking-associated hemodynamic and metabolic events. *N Engl J Med 1976;295:573–577.*

11. Weinberger MH. Antihypertensive therapy and lipids: paradoxical influences on cardiovascular disease risk. *Am J Med 1986;80:2A:64–70.*

12. Medical Research Council Working Party on Mild to Moderate Hypertension. Ventricular extrasystoles during thiazide treatment: substudy of MRC mild hypertension trial. *Br Med J 1983;287:1249–1253.*

13. Ames RP. Negative effects of diuretic drugs on metabolic risk factors for coronary heart disease: possible alternative therapies. *Am J Cardiol 1983;51:632–638.*

14. Murphy MB, Lewis PJ, Khoner EM, Schumer B, Dollery CT. Glucose intolerance in hypertensive patients treated with diuretics: a fourteen-year follow-up. *Lancet 1982;2:1293–1295.*

15. Osei K, Holland G, Falke JM. Indapamide: effect on apoprotein, lipoprotein, and glucoregulation in ambulatory diabetic patients. *Arch Intern Med 1986; 146:1973–1977.*

16. Mimran A, Zambrowski JJ, Coppolani T. The antihypertensive action of indapamide: result of a French multicentre study of 2,184 ambulant patients. *Postgrad Med J 1981;57:suppl 2:60–63.*

17. Harrower ADB, McFarlane G. Antihypertensive therapy in diabetic patients. The use of indapamide. *Am J Med 1988;84:1B:89–91.*

18. Holtzman E, Rosenthal T, Goldbourt U, Segal P. Do beta blockers alter lipids and what are the consequences? *J Cardiovasc Pharmacol 1987;10:suppl 2:S86–S92.*

19. Kannel WP, Castelli WP, Gordon T. Cholesterol in the prediction of athero-

sclerotic disease. New perspectives based on the Framingham Study. *Ann Intern Med 1979;90:85–91.*

20. Weimberger MH. Influence of an angiotensin converting enzyme inhibitor on diuretic-induced metabolic effects in hypertension. *Hypertension 1983;5:suppl III:132–138.*

21. Krone W, Muller-Wieland D, Nagele H, Behnke B, Gretan H. Effects of calcium antagonists and adrenergic antihypertensive drugs on plasma lipids and cellular cholesterol metabolism. *J Cardiovasc Pharmacol 1987;10:suppl 10:199–202.*

22. Lowenstein J, Neusy AJ. Effects of prazosin and propranolol on serum lipids in patients with essential hypertension. *Am J Med 1984;76:2A:79–84.*

23. Lund-Johansen P. The hemodynamics of essential hypertension. In: Robertson JIS, ed. Handbook of Hypertension. vol 1. Clinical Aspects of Essential Hypertension. *New York: Elsevier, 1983;151–172.*

24. Luque-Otero M, Rodrigo J, Alcazar J, Gabriel R, Fernandez-Pinilla C, Fernandez-Cruz A, Martell Claros N. Haemodynamics in children with blood pressure in the 95th percentile of the distribution. *J Hypertens 1987;5:suppl 5:435–437.*

25. Sowers JR. Hypertension in the elderly. *Am J Med 1987;82:1B:1–8.*

26. Lund-Johansen P. Handbook of Hypertension. vol 5. In: Birkenhager WH, Reid JL, eds. Clinical Pharmacology of Antihypertensive Drugs. *New York: Elsevier, 1984;39–66.*

27. Conway J, Lauwers P. Hemodynamic and hypotensive effects of long-term therapy with chlorothiazide. *Circulation 1960;21:21–27.*

28. Leenen FHH, Smith DL, Farkas RM, Boer WH, Reeves RA, Marquez-Julio A. Cardiovascular effects of indapamide in hypertensive patients with or without renal failure. *Am J Med 1988;84:1B:76–85.*

29. Man in't Veld AJ, Van den Meirecker AH, Schalekamp MA. Do beta blockers really increase peripheral vascular resistance? *Am J Hypertens 1988; 1:91–96.*

30. Sivertsson R. The hemodynamic importance of structural vascular changes in essential hypertension. *Acta Physiol Scand 1970;343:1–56.*

31. Folkow B. Physiological aspects of primary hypertension. *Phys Rev 1982; 62:347–504.*

32. Gribbin B, Pickering TG, Sleight P. Arterial distensibility in normal and hypertensive man. *Clin Sci 1979;56:413–417.*

33. Smulyan H, Vardan S, Griffiths A, Gribbin B. Forearm arterial distensibility in systolic hypertension. *JACC 1982;2:387–393.*

34. Safar ME, Pannier BM, London GM. Structural and functional modifications of peripheral large arteries in hypertensive patients. *J Clin Hypertens 1987;3:360–367.*

35. Sivertsson R, Hansson L. Effects of blood pressure reduction on the structural vascular abnormality in skin and muscle vascular beds in human essential hypertension. *Clin Sci Mol Med 1976;51:suppl 3:77–79.*

36. Svensson A, Gudbrandsson T, Sivertsson R, Hansson L. Haemodynamic effects of metoprolol and pindolol: a comparison in hypertensive patients. *Br J Clin Pharmacol 1982;13:259–267.*

37. Hansson L, Svensson A, Gudbrandsson T, Sivertsson R. Treatment of hypertension with beta blockers with and without intrinsic sympathomimetic activity. *J Cardiovasc Pharmacol 1983;5:suppl 1:26–29.*

38. Safar ME. Focus on the large arteries in hypertension. *J Cardiovasc Pharmacol 1985;7:suppl 2:1–4.*

Effects of Indapamide on Left Ventricular Mass and Function in Systemic Hypertension with Left Ventricular Hypertrophy

Michel Komajda, MD, Krystoff Klimczak, MD, Bernard Boutin, MD, François Brackman, MD, David Guez, MD, and Yves Grosgogeat, MD

Left ventricular hypertrophy (LVH) is frequently associated with hypertension and constitutes a major cardiovascular risk factor, the reduction of which should be considered when initiating antihypertensive therapy. To assess the effects of indapamide on LVH, 18 hypertensive patients were included in the study (11 men and 7 women, age 53.6 ± 2.9 years, mean ± standard deviation) whose supine diastolic blood pressure was greater than 95 mm Hg without (n = 11) or with (n = 7: 6 β blockers, 1 calcium antagonist) antihypertensive therapy. All presented with LVH, echocardiographically defined by a left ventricular mass index greater than 110 g/m². After a 2-week preinclusion period, all patients received indapamide, 2.5 mg/day, for a period of 6 months. Physical examination including blood pressure measurement was performed on selection (M-1/2), before (M0), and after 1 (M1), 3 (M3) and 6 (M6) months of indapamide treatment, and echocardiography was performed at M0 and M6. Quality of life was evaluated by means of questionnaires completed by the patient and the physician, and a visual analog scale was completed by the patient at M-1/2, M0 and M6. All clinical parameters remained stable during the 2-week preinclusion period. Indapamide administration induced a highly significant reduction in both supine systolic and diastolic blood pressures from 173.9 ± 2.9/100.5 ± 1.2 mm Hg at M0 to 150.9 ± 1.9/90.5 ± 1.3 mm Hg at M1 ($p < 0.001$), and 145.0 ± 1.7/86.0 ± 1.5 mm Hg at M6 ($p < 0.001$). Similar favorable effects were observed in the upright position.

Echocardiography showed a significant reduction in left ventricular mass index, from 174.4 ± 6.1 g/m² at M0 to 146.2 ± 6.0 at M6 ($p < 0.001$). Diastolic posterior wall thickness and interventricular wall thickness were significantly reduced from 12.0 ± 0.3/13.1 ± 0.4 mm at M0 to 10.9 ± 0.2/11.5 ± 0.3 mm at M6 ($p < 0.001$). Fractional shortening remained stable during treatment. The 2 quality of life questionnaires completed, respectively, by the patient and by the physician both evidenced a significant improvement during indapamide therapy; a general well-being score on visual analog scale increased from 5.4 ± 6.4 to 23.4 ± 6.4 ($p < 0.01$). Biochemical acceptability was satisfactory, with no significant changes in total cholesterol and high-density, low-density and very low density lipoprotein fractions.

These results show that indapamide exerts a significant antihypertensive activity with a good clinical acceptability and induces a beneficial reduction in left ventricular hypertrophy.

(Am J Cardiol 1990;65:37H–42H)

Indapamide is an orally active sulfonamide diuretic agent. It was commercialized more than 10 years ago, and it is currently prescribed all over the world and has proved to be an efficient and safe drug in patients with mild to moderate hypertension.[1]

Achieving normal blood pressure levels with a well-tolerated regimen remains the primary objective in the treatment of hypertensive patients, but can no longer be the only goal; an ideal antihypertensive drug must have beneficial effects on the other concomitant factors of cardiovascular morbidity and mortality.[2]

Left ventricular hypertrophy (LVH), which has been shown to be a common and early finding in patients with hypertension, appears to represent an additional and independent factor of poor prognosis. According to the Framingham study, LVH defined by either electrocardiographic or echocardiographic criteria is a powerful predictor of an increased risk of congestive heart failure, coronary artery disease and sudden death.[3–7]

For these reasons, there is a growing interest in antihypertensive drugs which, in addition to controlling blood pressure, also decrease left ventricular mass.[8,9]

In this study, we report results from an open trial undertaken to study the effects of indapamide on a specific group of hypertensive patients, all presenting with LVH.

METHODS

Patients: Patients who participated in this study were recruited and followed-up by several cardiologists working in private practice, and they were referred for an

From Hôpital Pitié-Salpétrière, Paris; IRIS 27, Neuilly-sur-Seine, France.

Address for reprints: Michel Komajda, MD, Hôpital Pitié-Salpétrière, 47 boulevard de l'Hôpital, 75651 Paris, France.

TABLE I General Characteristics of Patients

No. of patients	18
Sex ratio (M/F)	11/7
Mean age (years)	53.6 ± 2.9
Supine systolic blood pressure (mm Hg)	173.9 ± 2.9
Supine diastolic blood pressure (mm Hg)	100.5 ± 1.2
Left ventricular mass index (g/m^2)	174.4 ± 6.1

Values are mean ± standard error of the mean.

echocardiographic evaluation to the department of cardiology of the Hôpital Pitié-Salpétrière, Paris, France.

Subjects eligible for the trial were ambulatory patients of both genders, aged 30 to 75 years, with mild to moderate essential hypertension, as defined by a supine diastolic blood pressure between 95 and 115 mm Hg. They were either not previously treated or treated with β blockers but not controlled.

Noninclusion criteria were as follows: secondary hypertension; severe hypertension defined by a supine diastolic blood pressure greater than 115 mm Hg; complicated hypertension, i.e., coronary artery disease, heart failure, renal insufficiency, stage 3 or 4 fundus; presence of a metabolic disease (gout, insulin-dependent diabetes, noncontrolled noninsulin-dependent diabetes) or an hepatic disorder, or any other severe chronic disease; concomitant medication including corticosteroids, nonsteroidal antiinflammatory drugs, neuroleptics, antidepressants, lithium; and weight exceeded by 30% of the midpoint of recommended weight. In addition, patients in whom compliance appeared initially to be possibly poor or who had participated in a drug trial within the last 3 months did not enter the study.

Study design: The study was designed as an open study and conducted as follows: patients eligible were enrolled in a 2-week preinclusion period, during which they were either not treated or treated according to their previous regimen. This period was destined to confirm the stability of hypertension and the presence of an echocardiographic LVH.

At the end of this period, patients who fulfilled inclusion criteria and who had no exclusion criteria received indapamide at the daily dosage of 2.5 mg for a period of 6 months, either alone or in association with their previous treatment. A second echocardiographic evaluation was subsequently performed.

Blood pressure and heart rate: Blood pressure and heart rate were measured at the beginning of the study, at the time of inclusion, and after 1, 3 and 6 months of treatment.

Blood pressure was measured with a standard mercury sphygmomanometer. Supine blood pressure was recorded after 10 minutes of rest, and erect blood pressure after 2 minutes of standing. The mean of 3 measurements at 1-minute intervals was calculated. Diastolic blood pressure was defined as the point of disappearance of the Korotkoff sounds (phase V). Heart rate was measured by auscultation for 1 minute in similar conditions.

Echocardiography: M-mode echocardiography was performed with a Diasonics CV 400 echograph connected to a DRF recorder, a 3.5-MHz transducer at a paper speed of 50 mm/s. Patients were studied after 15 minutes at rest in the partial left decubitus position, with transducer placement in the third or fifth intercostal space. Transverse sweeps of the left ventricle were recorded at or just below the tip of the mitral leaflets.

Interventricular septal thickness (IVST), posterior wall thickness (PWT) and left ventricular internal diameter (LVID) were measured at end-diastole as defined by the onset of QRS complex on a simultaneous electrocardiogram. Thickness of the endocardial echoes was included in the measurement of IVST and PWT. Measurements were obtained from 4 cardiac cycles and then averaged.

Left ventricular mass was calculated according to the formula of Troy et al[10]: Left ventricular mass (g) = 1.05 $[(LVID + IVST + PWT)^3 - (LVID)^3]$. Left ventricular mass was then related to the body surface area and results were expressed as left ventricular mass index (g/m^2).

Left ventricular shortening fraction was calculated according to the following formula: SF = EDLVID − ESLVID/EDLVID, where EDLVID = end-diastolic left ventricular internal diameter and ESLVID = end-systolic left ventricular internal diameter.

Quality of life: Quality of life was assessed, as previously described,[11] using 3 different tests: a questionnaire filled in by the physician, a questionnaire completed by the patient and a visual analog scale. Both questionnaires consisted of multiple items under the following headings: appearance, contact, muscular and sensory fatigue, func-

TABLE II Supine and Standing Systolic and Diastolic Blood Pressure (BP) and Heart Rate at Baseline and at Various Intervals During Indapamide Treatment

	Baseline	1 Month	3 Months	6 Months	p*
Supine					
Systolic BP (mm Hg)	173.9 ± 2.9	150.9 ± 1.9	149.5 ± 1.7	145.0 ± 1.7	M0–M1, M3; M3–M6
Diastolic BP (mm Hg)	100.5 ± 1.2	90.5 ± 1.3	89.2 ± 1.4	86.0 ± 1.5	M0–M1, M3–6
Heart rate (beats/min)	67.0 ± 2.5	67.4 ± 2.2	65.8 ± 1.9	64.8 ± 3.1	
Standing					
Systolic BP (mm Hg)	171.7 ± 2.8	146.4 ± 2.2	143.7 ± 2.1	144.0 ± 2.4	M0–M1, M3, M6
Diastolic BP (mm Hg)	101.8 ± 1.2	91.9 ± 2.0	88.7 ± 1.6	86.8 ± 1.7	M0–M1, M3; M3–M6
Heart rate (beats/min)	69.7 ± 2.6	69.5 ± 2.3	69.5 ± 1.5	68.1 ± 2.2	

* $p < 0.001$.
Values are mean ± standard error of the mean.

tional visceral disorders, sleep, intellectual fatigue, emotion, mood, anxiety, vitality and personality. A score ranging from 0 (absence of symptoms) to 5 (according to the severity of the symptoms) was applied to each item. A visual analog scale provided another tool for evaluation of quality of life; it consisted of a horizontal straight line bearing 2 arrows, 1 at the left extremity indicating well-being, and 1 at the right extremity indicating ill-being. The patient had to answer to the question "how do you feel today?" by a cross on the axis.

Biochemical investigations: The following laboratory tests were performed at the beginning and at the end of the study: plasma electrolytes, creatinine, calcium, phosphate, urate, glycemia, total cholesterol, high-density lipoprotein, low-density lipoprotein and very low density lipoprotein cholesterol, and triglycerides. In addition, plasma electrolyte levels were measured after 1 month of treatment.

Statistical analysis: Statistical analysis was performed according to standard methods. The data are expressed as mean ± standard error of the mean. A 2-way analysis of variance (time-subjects) was used to assess the significance of changes in clinical, echocardiographic and biochemical variables during the study. When statistical significance was reached ($p < 0.05$), analysis was completed by a Newman-Keuls test for multiple comparisons of time points. Nonparametric data were analyzed by means of a Friedman test. Finally, Pearson's correlations between echocardiographic parameters and blood pressure data were studied.

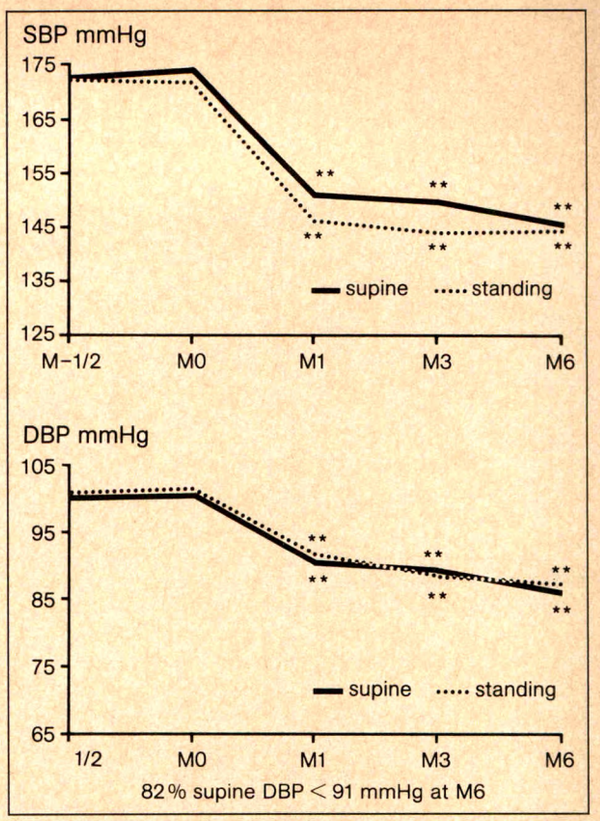


FIGURE 1. Effects of indapamide on supine and standing systolic (SBP) and diastolic (DBP) blood pressure after 3 and 6 months of treatment. **p <0.001.

RESULTS

All 18 patients entered into the study completed the trial. Their general characteristics are listed in Table I. Ages ranged from 30 to 73 years (mean 53.6) and all patients had mild to moderate essential hypertension, with a mean diastolic blood pressure of 100.5 mm Hg at the time of inclusion. Eleven were not previously treated and 6, although receiving β blockers or a calcium antagonist, were not equilibrated. Mean duration of hypertension was 4.1 ± 1.2 years.

Indapamide induced a significant reduction of both diastolic and systolic blood pressures (Table II). Mean reduction in the supine and standing positions was, respectively, 14.5 and 15 mm Hg for diastolic pressure and 28.9 and 27.7 mm Hg for systolic pressure. At the end of the study, 82% of patients achieved satisfactory blood pressure control, defined as a diastolic blood pressure below 90 mm Hg. Maximal antihypertensive effect was observed by 3 months and then remained stable (Fig. 1). No significant change in heart rate was observed during the study.

Electrocardiograms performed at the beginning of the study did not reveal any LVH in most of the patients, and no significant changes in electrocardiographic variables were observed during the study: mean Sokolow voltage was 3.3 ± 0.2 mV at the time of inclusion and after 6 months of treatment.

Echocardiographic parameters are listed in Table III. At the time of inclusion, IVST of 11 mm or more was observed in 16 patients and the PWT was 11 mm or more in 16 patients, left ventricular internal dimension exceeded 50 mm in 8 patients, and left ventricular mass and left ventricular mass index were elevated in all the patients.

We observed a decrease of these parameters throughout the study. This decrease reached levels of statistical significance for left ventricular PWT, IVST, left ventricular mass and left ventricular mass index. PWT decreased from 12 ± 0.3 to 10.9 ± 0.2 mm ($p < 0.001$), IVST from 13.1 ± 0.4 to 11.5 ± 0.3 mm ($p < 0.001$), left ventricular mass from 332.79 ± 14.69 to 279.25 ± 13.35 g ($p < 0.001$), and left ventricular mass index from 174.42 ± 6.13 to 146.25 ± 6.04 g/m^2 ($p < 0.001$) (mean reduction of 16%). Reduction of left ventricular mass index was

TABLE III End-Diastolic Echocardiographic Parameters at Baseline and After Six Months of Indapamide Treatment

	Baseline	6 Months
PWT (mm)	12.00 ± 0.30	10.90 ± 0.20*
IVST (mm)	13.10 ± 0.40	11.50 ± 0.30*
LVID (mm)	51.70 ± 1.20	50.20 ± 1.70
LVM (g)	332.79 ± 14.69	279.25 ± 13.35*
LVMI (g/m^2)	174.42 ± 6.13	146.25 ± 6.04*
EF (%)	38.30 ± 0.80	38.10 ± 0.60

* $p < 0.001$.
Values are mean ± standard error of the mean.
EF = ejection fraction; IVST = interventricular septal thickness; LVID = left ventricular interval diameter; LVM = left ventricular mass; LVMI = left ventricular mass index; PWT = posterior wall thickness.

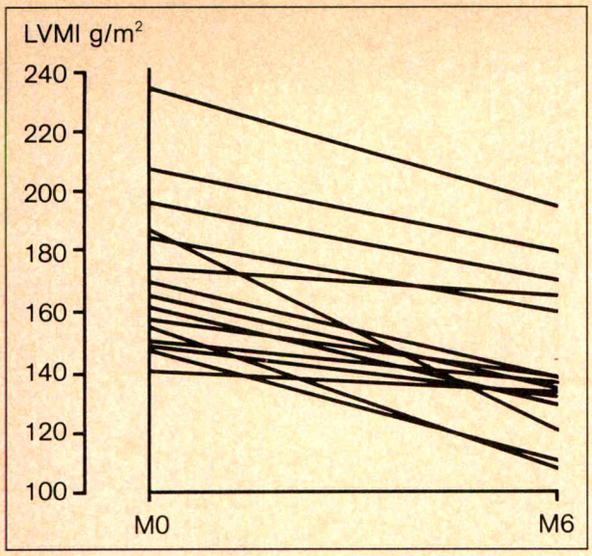


FIGURE 2. Individual changes of left ventricular mass index (LVMI) after 6 months with indapamide treatment.

observed in almost all the patients (Fig. 2). Conversely, end-diastolic internal ventricular diameter did not change significantly during therapy (from 51.7 ± 1.2 to 50.2 ± 1.7 mm). Mean left ventricular shortening fraction was 38.3 ± 0.8% and remained stable after 6 months of treatment.

Significant correlation was found between IVST, left ventricular mass, left ventricular mass index and supine systolic blood pressure at the beginning of the study (Table IV). No correlation was found between variation of echocardiographic parameters and reduction of supine systolic or diastolic blood pressure.

Quality of life improved with indapamide therapy, as confirmed by the results of both questionnaires: mean score decreased from 8.1 ± 1.6 to 5.2 ± 1.4 ($p < 0.001$) for the physician's questionnaire and from 13.5 ± 2.7 to 7.4 ± 2.2 ($p < 0.001$) for the patient's questionnaire. In addition, mean score from the visual analog scale increased from 5.4 ± 6.4 to 23.4 ± 6.4 ($p < 0.01$). Improvement was particularly significant for the following items (Fig. 3): anxiety (a primordial factor in the stability of blood pressure of hypertensive patients), sleep disorders (difficulty in getting to sleep, frequent awakening during the night, difficulty in wakening, nightmares, diurnal drowsiness) and personality (sensitiveness, irritability, contrariness, aggressiveness and anger). Moreover, overall well-being was greatly improved if one considers the results of the visual analog scale before and after indapamide treatment: 5.4 ± 6.4 and 23.4 ± 6.4 ($p < 0.01$).

TABLE IV Correlation Between Baseline End-Diastolic Echocardiographic Anatomic Parameters and Supine Systolic (SSBP) and Diastolic Blood Pressure (SDBP)

	SSBP	SDBP
PWT	0.453	0.261*
IVST	0.570*	0.517
LVID	0.136	0.128
LVM	0.544*	0.414
LVMI	0.670†	0.387

* $p < 0.05$; † $p < 0.01$.
Abbreviations as in Table III.

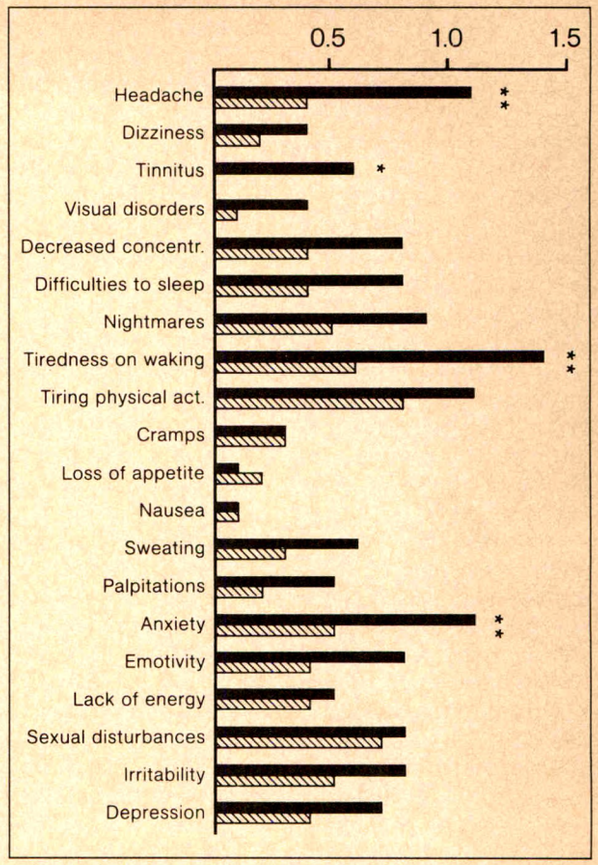


FIGURE 3. Quality of life assessed by patient's questionnaires. *p <0.05; **p <0.01.

With regard to biochemical parameters, the only significant change was plasma potassium (mean decrease 0.35 mmol/liter). No alterations of lipid profile were observed (Table V), and plasma uric acid increased slightly without reaching statistical significance and remained within the normal range in every case.

DISCUSSION

Regression of left ventricular mass with indapamide therapy was first suggested several years ago by Rowlands et al[12] who demonstrated a significant regression of left ventricular mass index in 24 patients treated with various agents, 3 of whom were being treated with indapamide. Subsequently, Mace et al[13] reported a 6% reduction of left ventricular mass index observed in 5 patients treated with indapamide for a period of 4 months; all these patients had mild to moderate essential hypertension, were not previously treated, and did not have LVH at the beginning of the study. The present study confirms that indapamide, in addition to providing satisfactory blood pressure control, induces a highly significant regression of left ventricular mass index and extends the results to a specific high risk population of hypertensive patients.

Interestingly, the reduction of left ventricular mass index that was observed in this study was due only to a reduction of wall thickness because there was no variation of left ventricular internal diameter. Moreover, the reduction was homogeneous if one considers the similar decrease of IVST and PWT. Patients who demonstated the greatest reduction in left ventricular mass index appeared to have the largest initial LVH; this may explain the difference in the mean degree of reduction observed in this trial and the one conducted by Mace et al.[13]

Other antihypertensive agents, with the exception of vasodilators and diuretics, have been shown to have positive influence on left ventricular mass.[14] Even if there is a great heterogeneity in the design of these trials, indapamide would appear to be among the drugs that have the most potent effects on left ventricular mass reduction. Only double-blind parallel studies, which are currently being undertaken, can confirm this theory.

All of the patients had normal left ventricular end-diastolic dimension and left ventricular ejection fraction not only at the beginning of the study but also after indapamide treatment. This attests to normal systolic function and confirms previous studies conducted with indapamide in hypertensive patients without LVH.[15,16] Moreover, it is in agreement with trials performed with other antihypertensive agents in patients with LVH.[17,18] Study of diastolic performance would be more interesting, as it has been shown by various means (Doppler echocardiography, magnetic resonance imaging, radionuclide angioventriculography) that impairment occurs earlier in the ventricle that becomes hypertrophic in response to a chronic pressure overload.[19–21] This point is currently under investigation in other trials.

The correlation between LVH and supine systolic blood pressure that we observed at the beginning of the study was stronger than that frequently reported and confirms that the blood pressure level is at least one of the factors that determines LVH. Obviously, pressure overload cannot be the sole factor, because, as previously described with other drugs, no correlation was found between reduction of blood pressure and decrease in left ventricular mass after indapamide therapy. A number of other factors are thought to interfere with the development or the regression of LVH[22]: stimulation of the sympathetic nervous system, activation of the renin-angiotensin system, various trophic agents and genetic predisposition. The role of these factors is often increased when trying to explain the discrepancy between positive effects observed with drugs like adrenergic inhibitors, converting enzyme inhibitors and β blockers, and the absence of effects observed with vasodilators or diuretics.[23,24]

Previous studies have shown that indapamide achieves its antihypertensive effect mainly through peripheral vasodilation but does not exert any stimulation of adrenergic activity.[25] This particular characteristic, which has helped to individualize indapamide in the family of diuretics, may account for the present efficacy of this drug. Conversely, as angiotensin II has emerged as a powerful determinant of left ventricular adaptation,[26] it is worth noting that an activation of the renin-angiotensin system has been regularly observed in patients receiving indapamide.[25]

TABLE V Biochemical Parameters During Indapamide Treatment

Parameters	Baseline	6 Months
Creatinine (μmol/liter)	89.00 ± 3.80	90.00 ± 5.20
Uric Acid (μmol/liter)	311.00 ± 27.20	358.00 ± 30.00
Sodium mmol/liter	140.00 ± 0.80	140.00 ± 0.08
Potassium mmol/liter	4.38 ± 0.08	4.03 ± 0.08*
Total cholesterol mmol/liter	5.80 ± 0.30	5.90 ± 0.30
HDL cholesterol mmol/liter	1.40 ± 0.10	1.40 ± 0.08
LDL cholesterol mmol/liter	3.30 ± 0.30	3.30 ± 0.40
VLDL cholesterol mmol/liter	0.40 ± 0.30	0.40 ± 0.08
Triglycerides mmol/liter	1.40 ± 0.40	1.50 ± 0.40

* $p < 0.01$.
Values are mean ± standard error of the mean.
HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low density lipoprotein.

Diuretics have been used for many years as the main treatment for patients with mild to moderate essential hypertension and, according to the last recommendations of the American Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure, they remain a major alternative as "first step" drugs.[2] When new drugs became available during the early 1980s, several questions were raised concerning the safety of diuretics as antihypertensive agents, one of the major points being the deleterious effect of diuretics on lipoprotein metabolism. At that time, we demonstrated that indapamide, although belonging to the diuretic family, did not alter lipid metabolism even in patients with previous lipid disorders.[27] The present study suggests that indapamide has a positive effect on LVH, one of the major prognostic factors in hypertensive patients both simultaneously and independently of its control of blood pressure levels.

REFERENCES

1. Chaffman M, Heel RC, Brogden RN, Speight TM, Avery GS. Indapamide. A review of its pharmacodynamic properties and therapeutic efficacy in hypertension. *Drugs 1984;28:189–235.*

2. 1988 Joint National Committee. The 1988 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med 1988;148:1023–1038.*

3. Kannel WB. Prevalence and natural history of electrocardiographic left ventricular hypertrophy. *Am J Med 1983;75(3A):4–11.*

4. Casale PN, Milner M, Devereux RB, Zullo G, Harshfield G, Pickering TG, Spitzer MC, Laragh JH. Value of echocardiographic left ventricular mass in predicting cardiovascular morbid events in hypertensive men. *Circulation 1985; 72:suppl III:III-130.*

5. Levy D, Savage DD, Garrisson RJ, Anderson KM, Kannel WB, Castelli WP. Echocardiographic criteria for left ventricular hypertrophy: the Framingham Heart Study. *Am J Cardiol 1987;59:956–960.*

6. Levy D, Anderson KM, Savage DD, Kannel WB, Christiansen JC, Castelli WP. Echocardiographically detected left ventricular hypertrophy: prevalence and risk factors: the Framingham Heart Study. *Ann Intern Med 1988;108:7–13.*

7. Levy D. Left ventricular hypertrophy. Epidemiological insights from the Fra-

mingham Heart Study. *Drugs 1988;35:suppl 5:1–5.*
8. Tarazi RC. The heart in hypertension. *N Engl J Med 1985;312:308–309.*
9. Massie BM, Tubau JF, Szlachic J, O'Kelly BF. Hypertensive heart disease: the critical role of left ventricular hypertrophy. *J Cardiovasc Pharmacol 1989; 13:suppl 1:S18–S24.*
10. Troy BL, Pombo J, Rackely CE. Measurement of left ventricular wall thickness and mass by echocardiography. *Circulation 1972;45:602–609.*
11. Guez D, Crocq L, Safavian A, Labardens P. Effects of indapamide on the quality of life of hypertensive patients. *Am J Med 1988;84:53–59.*
12. Rowlands DB, Glover DR, Ireland MA, McLeay M, Stallard TJ, Watson RDS, Littler WA. Assessment of left ventricular mass and its response to antihypertensive treatment. *Lancet 1982;1:467–470.*
13. Mace PJE, Littler WA, Glover DR, Rowlands DB, Stallard TJ. Regression of left ventricular hypertrophy in hypertension: comparative effects of three different drugs. *J Cardiovasc Pharmacol 1985;7:S52–S55.*
14. Messerli FH, Oren S, Grossman E. Left ventricular hypertrophy and antihypertensive therapy. *Drugs 1988;35:suppl 5:27–33.*
15. Dunn FG, Hillis WS, Tweddel A, Rae AP, Lorimer AR. Noninvasive cardiovascular assessment of indapamide in patients with essential hypertension. *Postgrad Med J 1981;57:suppl 2:19–22.*
16. Horgan JH, O'Donovan A, Teo KK. Echocardiographic evaluation of left ventricular function in patients showing an antihypertensive and biochemical response to indapamide. *Postgrad Med J 1981;57:suppl 2:64–67.*
17. Dunn F, Ventura HO, Messerli FH, Kobrin I, Frohlich E. Time course of regression of left ventricular hypertrophy in hypertensive patients treated with atenolol. *Circulation 1987;76:254–258.*
18. Strauer BE, Mahmoud MA, Bayer F, Bohn I, Motz U. Reversal of left ventricular hypertrophy and improvement of cardiac function in man by nifedipine. *Eur Heart J 1984;5:suppl F:53–60.*
19. Fouad FM, Slominski JM, Tarazi RC. Left ventricular diastolic function in hypertension: relation to left ventricular mass and systolic function. *JACC 1984;3:1500–1506.*
20. Shapiro LM, Gibson DG. Patterns of diastolic dysfunction in left ventricular hypertrophy. *Br Heart J 1988;59:438–445.*
21. Trimarco B, De Luca N, Ricciardeli B, Rosiello G, Volpe M, Condorelli G, Lembo G, Condorelli M. Cardiac function in systemic hypertension before and after removal of left ventricular hypertrophy. *Am J Cardiol 1988;62:745–750.*
22. Dahlöf B. Factors involved in the pathogenesis of hypertensive cardiovascular hypertrophy: a review. *Drugs 1988;35:suppl 5:6–26.*
23. Drayer JIM, Gardin JM, Weber MA, Aronow WS. Changes in ventricular septal thickness during diuretic therapy. *Clin Pharmacol Ther 1982;32:283–288.*
24. Leenen FH, Smith DL, Farkas RM, Reeves RA, Marquez-Julio A. Vasodilators and regression of left ventricular hypertrophy—hydralazine versus prazosin in hypertensive humans. *Am J Med 1987;82:969–978.*
25. Campbell DB. The possible mode of action of indapamide. A review. *Curr Med Res Opin 1983;8:suppl 3:9–24.*
26. Schmieder RE, Messerli FH, Garavaglia GE, Nunez BD, MacPhee AA. The renin angiotensin aldosterone system (RAAS) modulates myocardial hypertrophy in essential hypertension (abstr). *Circulation 1987;76:suppl IV:IV-440.*
27. Gerber A, Weidmann P, Bianchetti MG, Ferrier C, Laederach K, Mordasini R, Riesen W, Bachmann C. Serum lipoproteins during treatment with the antihypertensive agent indapamide. *Hypertension 1985;7:suppl II:164–169.*

Role of Metabolic Risk Factors in Cardiovascular Prognosis of Systemic Hypertension

William J. Louis, MD, Laurence G. Howes, PhD, Nora Straznicki, BPharm, Henry Krum, MB, BS, Paddy Phillips, DPhil, Jillian Broadbear, BSc, and John J. McNeil, PhD

There is an increasing awareness of the need to manage multiple risk factors in hypertensive patients, and of possible adverse metabolic effects of antihypertensive drugs which may counteract their ability to reduce the risk of cardiovascular disease. Data collected from the Austin Hospital Hypertension Clinic support previous observations that the incidence of cardiovascular risk factors such as plasma lipid abnormalities are high in hypertensive patients, and although it is becoming easier to control blood pressure in these patients, modification of other risk factors is difficult. The use of diuretics in doses lower than those conventionally prescribed has been advocated as a means of reducing the adverse metabolic effects. However, data from this study suggest that although low-dose hydrochlorothiazide therapy (25 to 50 mg/day) may be as effective as conventional doses of captopril in reducing blood pressure, adverse metabolic effects on plasma potassium, glucose and uric acid levels remain a problem. Indapamide, a relatively new diuretic when used at a fixed dose (2.5 mg/day), appears to be devoid of significant adverse metabolic effects and is a useful alternative to thiazide diuretics. An integrated approach to the management of multiple cardiovascular risk factors is important in hypertensive patients and should include nonpharmacologic methods and the selection of antihypertensive drugs that do not have adverse metabolic effects.

(Am J Cardiol 1990;65:43H–45H)

From the Department of Medicine, University of Melbourne, Melbourne, Australia; Clinical Pharmacology and Therapeutics Unit, Austin Hospital, Heidelberg, Australia; Department of Social and Preventative Medicine, Monash University, Alfred Hospital, Prahran, Australia. This study was supported by a grant from the National Heart Foundation of Australia, Canberra, Australia.

Address for reprints: Professor William J. Louis, MD, Clinical Pharmacology and Therapeutics Department, Heidelberg, Victoria 3084, Australia.

Preventive public health measures that address multiple cardiovascular risk factors including hypertension have already contributed to an impressive decrease in mortality from coronary artery disease and incidence of stroke in the United States and Australia.[1] Interventions include attempts to modify diet, smoking and exercise habits. Hypertension newly diagnosed in a significant number of patients may well be controlled without drug therapy, and hypertension in many more patients will be controlled with simpler drug regimens as well as new drug therapies.

INCIDENCE OF MULTIPLE RISK FACTORS

We have previously reported the incidence of a range of risk factors in patients attending the Austin Hospital Hypertension Clinic during 1986 and 1987.[1] We can now update some of this information with data obtained from a survey of 187 patients from this same clinic in 1988 and for whom data from 1987 were also available. Table I summarizes the percentage of patients in 1987 and 1988 with diastolic blood pressures <90, 95 and 100 mm Hg. It appears that in 1988, a 12-month period in which there was both attention to multiple risk factor modification and the introduction of newer forms of therapy such as low-dose diuretics, angiotensin-converting enzyme inhibitors and calcium antagonists, improvement in blood pressure control was achieved in the clinic with an increased percentage of patients having diastolic blood pressures <90 mm Hg.

It is interesting to compare these data with reports[2–5] of diastolic blood pressure control from other centers (Table II). This confirms that hypertension in increasing numbers of patients now seem to be better controlled. Andersson et al[3] reported that 52% of patients in their clinic had diastolic blood pressures >95 mm Hg in 1978 and Degoulet et al[2] reported 27% in 1983, whereas the figure in our clinic in 1988 was around 12%. We have also examined alcohol consumption and smoking in this group of patients. Overall, there has been a small decrease in alcohol consumption in the male population in the 1987/1988 period and a significant change in the number of smokers ($p < 0.25$).

METABOLIC EFFECTS OF ANTIHYPERTENSIVE THERAPY

Another concern in patients taking long-term antihypertensive medication is that unwanted alterations in risk factors such as plasma lipid levels and glucose tolerance may cancel the benefits of blood pressure reduction, particularly in relationship to the development of atheroscle-

TABLE I Control of Supine Diastolic Blood Pressure in a Hypertension Clinic (Austin Hospital 1987, 1988)

Diastolic Blood Pressure (mm Hg)	% of Patients (n = 277) 1987	1988
<90	66.4	79.9
<95	81.2	88.2
<100	91.3	96.4

TABLE II Control of Diastolic Blood Pressure (BP) in Other Centers

No. of Pts.	Mean ± SD Diastolic BP (mm Hg)	% Patients DBP >95 mm Hg	Reference
981	87.7 ± 11.0	27	2
646	97 ± 9.8	52	3
5,485	87.6	—	4
257	—	32	4

DBP = diastolic blood pressure; SD = standard deviation.

TABLE III Plasma Total Cholesterol and High-Density Lipoprotein Cholesterol Levels in 181 Patients

	Total Cholesterol (mmol/liter) 1987	1988	HDL Cholesterol (mmol/liter) 1987	1988
Total	5.99 ± 1.13	5.97 ± 1.13	1.20 ± 0.45	1.27 ± 0.38*
Men	5.81 ± 1.06	5.76 ± 1.10	1.08 ± 0.38	1.15 ± 0.33
Women	6.15 ± 1.17	6.17 ± 1.13	1.29 ± 0.48	1.37 ± 0.39

* $p < 0.05$ compared with 1987 levels (Student paired *t* test).
HDL = high-density lipoprotein.

TABLE IV Biochemical Changes (mmol/liter) After Treatment with Captopril or Hydrochlorothiazide (HCT)

	Glucose	Potassium	Uric Acid
Baseline	4.77 ± 1.36	3.72 ± 0.33	0.30 ± 0.10
Captopril	4.85 ± 0.55	3.64 ± 0.30	0.33 ± 0.12
HCT	5.12 ± 0.73*	3.24 ± 0.26*	0.38 ± 0.13*

* $p < 0.05$ compared with captopril treatment (Student paired *t* test).

TABLE V Changes in Lipid Fractions (mmol/liter) During Treatment with Captopril or Hydrochlorothiazide (HCT)

	Captopril	HCT	Control
Total cholesterol (n = 20)	6.12 ± 1.11	6.36 ± 0.95	6.20 ± 0.85
HDL cholesterol (n = 20)	1.37 ± 0.41	1.39 ± 0.46	1.59 ± 0.36
Triglycerides (n = 15)	1.26 ± 0.50*	1.09 ± 0.40	0.98 ± 0.28

* $p < 0.05$ compared with control (Student paired *t* test).

rosis. Since 1986, the percentage of both women and men with cholesterol levels greater than 5.5 mmol/liter has fallen. In 1986, the figure for men was 56.5% and for women 78.5%. In 1987, it had fallen to 52.7 and 72.7% and in 1988 to 51.2 and 68.7%, respectively. It is disappointing, however, that the change has not been greater since there has been a fairly intensive program undertaken to identify patients with elevated cholesterol levels and to modify them by dietary means, and if necessary by cholestyramine therapy, after referral to and reinforcement by the hospital dietician. Table III summarizes changes in plasma total cholesterol and high-density lipoprotein cholesterol levels in these patients in 1987 and 1988. The overall figures for cholesterol, however, are somewhat deceptive. In fact, mean cholesterol levels have not changed and most of the decrease in percentage has been the result of changes in cholesterol levels in the group treated with cholestyramine. Total cholesterol decreased from 7.63 ± 1.37 in 1987 to 6.53 ± 0.8 mmol/liter in 1988 in the cholestyramine-treated group (n = 15), whereas cholesterol did not change (5.80 ± 1.02 to 5.94 ± 1.16 mmol/liter) in patients not taking cholestyramine (n = 169) in 1988. The small but significant increase in levels of high-density lipoprotein cholesterol from 1.17 ± 0.43 to 1.27 ± 0.38 mmol/liter ($p < 0.05$) was more encouraging.

One of the more interesting developments in treatment has been the move to administer smaller doses of diuretics both as monotherapy and in combination with other antihypertensive agents.[6] Thiazides have now been in use for nearly 30 years; they are simple to use and effective and can easily be combined with other forms of therapy. Their main disadvantages have been their adverse metabolic effects[1] and that, in higher doses, they may produce impotence.[7] To a large extent, many of these metabolic effects can be overcome by doses that are half or less of the conventional dose regimens. At these doses, effects on plasma lipids, blood sugar and other biochemical parameters are believed to be minimized.

We have examined some of these propositions in a double-blind crossover study of 20 hypertensive subjects, aged 41 to 73 years, with supine diastolic blood pressures of 90 to 110 mm Hg after a 2-week placebo run-in phase. These subjects had total cholesterol levels that were mildly elevated (5.7 to 8.7 mmol/liter). Subjects were studied over 2 treatment periods during which they received either captopril or hydrochlorothiazide. Wash-out periods of 14 days preceded, divided and followed the 2 treatment periods, the order of which was randomized. Each treatment period lasted 8 weeks. According to the randomization, subjects were assigned to either captopril, 25 mg twice daily, or hydrochlorothiazide, 12.5 mg twice daily. During the fourth week of treatment the drug dosage was doubled for the remaining treatment period if the patients' blood pressure was >95 mm Hg diastolic. As a result, blood pressure control was maintained in 10 patients taking 25 mg and in 10 taking 50 mg of hydrochlorothiazide daily and in 11 patients taking 50 mg and a further 9 taking 100 mg of captopril daily.

In this study, patients taking hydrochlorothiazide had a small decrease in weight, significant elevations in plasma glucose and uric acid, and significant reductions in serum potassium compared with treatment with an an-

giotensin-converting enzyme inhibitor (Table IV). Fifteen patients required potassium supplementation during the diuretic treatment phase and none during treatment with captopril. There were no differences in plasma cholesterol concentrations between the 2 forms of treatment. However, plasma triglycerides were significantly elevated in the captopril group compared with baseline, and the difference between triglyceride levels during captopril and hydrochlorothiazide therapy almost achieved statistical significance (Table V). This adverse effect on triglycerides has not been previously reported, and in this respect treatment with captopril appears to resemble that of propranolol.

We were not able to establish a clear-cut increase in the metabolic risk factors in patients whose dose of hydrochlorothiazide increased from 25 to 50 mg, except that 3 of the 11 patients who were taking 50 mg/day had potassium levels of ≤3.0 mmol/liter. Potassium levels <3.2 mmol/liter were not seen in the lower-dose diuretic group. Overall, the data indicate that reducing the dose of hydrochlorothiazide to 25 mg/day does not overcome the metabolic changes associated with diuretic therapy. Blood pressure control was similar during the 2 treatment regimens, which indicates that the doses of hydrochlorothiazide are equally as effective as the doses used during captopril therapy.

INDAPAMIDE

To avoid the problems of adverse metabolic changes during diuretic therapy, the use of lower doses is advised. One compound that is being looked at carefully with regard to adverse metabolic effects is the relatively new agent indapamide. When used at a fixed dose of 2.5 mg/day, it has an effective antihypertensive action and does not appear to have the usual pattern of adverse biochemical and endocrine effects seen with other diuretics. This may reflect the fact that indapamide differs structurally from chlorthalidone, hydrochlorothiazide and furosemide by possessing an isoindoline methyl substituent. Alternatively, this lack of adverse effects may be a result of the low dose of 2.5 mg/day.[8] There is considerable evidence that in both nondiabetic and diabetic patients, indapamide does not interfere with either glucose use or insulin release,[9–11] and in long-term therapy it does not show evidence of having adverse effects on total cholesterol or lipid fractions.[12–15] It appears, therefore, that by administering low doses of indapamide it is possible to achieve an effective vasodilator action without producing the adverse biochemical effects on lipoprotein metabolism and blood glucose that usually accompany thiazide diuretic therapy. This does not mean that the drug is totally free of adverse effects. Like the long-acting thiazide diuretic chlorthalidone,[16] when used in doses above the recommended 2.5 mg/day, it can produce hypokalemia.[8] Although hypokalemia occurs infrequently in patients given the recommended dose, it is important to ensure that patients are potassium replete before commencing therapy and to avoid therapy in patients who have a known tendency to lose potassium.

It is possible that a similar absence of adverse metabolic effects may be achieved by using even lower doses of conventional thiazide diuretics. However, from the studies reported here, it appears that hydrochlorothiazide must be given at a dose of <25 mg/day to avoid adverse effects on glucose, potassium and uric acid, and it remains to be established whether lower doses (e.g., 12.5 mg/day) provide effective hypotensive therapy without these adverse metabolic changes.

CONCLUSION

The recognition of the importance of multiple cardiovascular risk factors, including hypertension, and the introduction of preventive public health measures to address them in combination with improved medical care, have already contributed to an impressive decrease in mortality from coronary artery disease in the United States and Australia.

Medical practitioners are directing increasing amounts of time and resources toward attempts to modify diet, smoking and exercise habits. With proper attention to these aspects, hypertension newly diagnosed in a significant number of patients may be well controlled without drug therapy, and hypertension in many more patients will be controlled with simpler drug regimens as well as new drug therapies. The recognition that traditional drugs such as diuretics can be used effectively in lower doses with less risk of adverse metabolic effects is a significant advance in the management of hypertension.

REFERENCES

1. Howes LG, Louis WJ. Effects of antihypertensive drugs on cardiovascular risk factors. *Clin Exp Pharmacol Physiol 1988;15:199–202.*

2. Degoulet P, Menard J, Vu HA, Golmard JL, Devries C, Chatellier G, Ploud PF. Factors predictive of attendance at clinic and blood pressure control in hypertensive patients. *Br Med J 1983;287:88–93.*

3. Andersson O, Berglund G, Hansson L, Sunnerstedt R, Sivertsson R, Wikstrand J, Wilhelmsen L. Organization and efficacy of an outpatient hypertension clinic. *Acta Med Scand 1978;203:391–398.*

4. Hypertension, Detection and Follow-up Program Cooperative Group. Patient participation in a hypertension control program. *JAMA 1978;239:1507–1514.*

5. Petrie JC, Rob OJ, Webster J, Scott AK, Jeffers TA, Park MD. Computer assisted shared care in hypertension. *Br Med J 1985;290:1960–1962.*

6. Louis WJ. The use of diuretics in the treatment of hypertension. *Aust Prescriber 1975;1:3–5.*

7. Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *Br Med J 1985;291:97–104.*

8. Louis WJ, Howes LH, Krum H. Facteurs de risque métaboliques et hypertension. In: Tables Rondes: Traitement de la Maladie Hypertensive. *Expansion Scientifique Francais, Paris, 1988;245–246.*

9. Raggi U, Palumbo P, Moro B, Bevilacqua M, Norbiato G. Indapamide in the treatment of hypertension in non-insulin-dependent diabetes. *Diabetes Hypertens 1985;7:157–160.*

10. Houston MC. The effects of antihypertensive drug on glucose intolerance in hypertensive nondiabetics and diabetics. *Am J Cardiol 1988;115:640–656.*

11. Harrower ADB, McFarlane G, Donnelly T, Gray CE. Effect of indapamide on blood pressure and glucose tolerance in non-insulin-dependent diabetics. *Diabetes Hypertens 1985;1:161–163.*

12. Beling S, Vukovich RA, Neiss ES, Zisblatt M, Webb E, Losi M. Long term experience with indapamide. *Am Heart J 1983;106:258–262.*

13. Ferrara LA, Giumetti D, Fasano ML, Soro S, Januzzi A, Strazzullo P, Mancini M. Once a day indapamide therapy in hypertension. Effects on the heart and peripheral arterial circulation. *Jpn Heart J 1983;24:731–737.*

14. Scalabrino A, Galeone F, Giuntoli F. Clinical investigation on long term effects of indapamide in patients with essential hypertension. *Curr Ther Res 1984;35:17–22.*

15. Meyer-Sabellek W, Gotzen R, Heitz J, Arntz HR, Schultz KL. Serum lipoprotein levels during long-term treatment of hypertension with indapamide. *Hypertension 1985;7:6(2):170–174.*

16. Louis WJ, Doyle AD, Dawborn JK, Johnston CI. A comparison of chlorothiazide, chlorthalidone and cyclopenthiazide in the treatment of hypertension. *Med J Aust 1973;2(1):23–25.*

Efficacy of Antihypertensive Treatment with Indapamide in Patients with Noninsulin-Dependent Diabetes and Persistent Microalbuminuria

Sergio Gambardella, MD, Simona Frontoni, MD, Maria Grazia Felici, MD, Vincenza Spallone, MD, Patrizia Gargiulo, MD, Susanna Morano, MD, and Guido Menzinger, MD

In patients with insulin-dependent diabetes, antihypertensive treatment has a beneficial effect on the rate of progression toward uremia of overt diabetic nephropathy (albumin excretion rate [AER] >300 mg/24 hour). The influence of hypertension on the progression of "incipient" nephropathy (AER ranging between 30 and 300 mg/24 hours) is not well defined, particularly in patients with noninsulin-dependent diabetes. In this study, 21 patients with noninsulin-dependent diabetes and hypertension (11 with normoalbuminuria and 10 with microalbuminuria), who were comparable for age, duration of diabetes and hypertension, were treated with indapamide, 2.5 mg once daily, and followed up for 24 months. Blood pressure, glomerular filtration rate (GFR), albumin excretion rate and subclass 4 of urinary immunoglobulin G (IgG_4) were indicated.

In normoalbuminuric patients, blood pressure was significantly reduced, whereas AER, IgG_4 and GFR did not show any variation throughout the study. In microalbuminuric patients, blood pressure, AER and IgG_4 were significantly reduced, and GFR remained unchanged. In patients with noninsulin-dependent diabetes, antihypertensive treatment, which is begun during incipient diabetic nephropathy, may have a beneficial effect on the progression of the disease, although a long-term follow-up study is needed to confirm this.

(Am J Cardiol 1990;65:46H–50H)

From Malattie del Ricambio, Department of Internal Medicine, University of Rome "Tor Vergata"; Endocrinology I (Clinica Medica 2), University of Rome "La Sapienza," Rome Italy.

Address for reprints: Sergio Gambardella, MD, Malattie Metaboliche, Complesso Integrato Columbus, Via della Pineta Sacchetti, 506 00168 Rome, Italy.

Diabetes mellitus and hypertension are commonly associated diseases. It is now accepted that treatment of hypertension will have a beneficial long-term effect on the rate of deterioration of renal function in all kinds of renal diseases.[1] Long-term studies have been performed only in insulin-dependent patients with overt nephropathy, in whom antihypertensive treatment has produced a beneficial effect on renal function.[2,3] Hypertension is, however, frequently present in patients with noninsulin-dependent diabetes who present either a high incidence of nephropathy or a similar risk of renal failure to that in insulin-dependent diabetics.[4] Nevertheless, there have been few studies on the influence of antihypertensive treatment on the progression of clinical or "incipient nephropathy," or both, in patients with noninsulin-dependent diabetes.

The objectives of the study were to determine the effect of treatment of raised arterial blood pressure on the glomerular filtration rate (GFR), albumin excretion rate (AER) and subclass 4 of urinary immunoglobulin G (IgG_4) (recently proposed as a new marker of diabetic nephropathy) in patients with noninsulin-dependent diabetes and hypertension with and without microalbuminuria.

METHODS

Twenty-one patients with noninsulin-dependent diabetes and hypertension were entered into the study. They were grouped according to the daily urinary excretion of albumin (three 24-hour urine samples collected at home): 11 had normoalbuminuria (AER <30 mg/24 hours), mean age 49.5 years (range 45 to 54), mean duration of diabetes 7.5 years (range 6.5 to 9.5), mean duration of hypertension 9.5 years (range 7.5 to 11), body mass index <30 kg/m^2 (group 1); 10 had microalbuminuria (AER ranging between 30 and 300 mg/24 hours), mean age 51 years (range 44.5 to 56), mean duration of diabetes 8.5 years (range 7 to 9.5), mean duration of hypertension 10 years (8.5 to 11), body mass index <30 kg/m^2 (group 2). The latter were classified as having incipient diabetic nephropathy according to the following criteria: persistent microalbuminuria, sterile urine without ketonuria (<2+), duration of diabetes more than 5 years and no history of kidney or urinary tract disease.[5]

Informed consent was obtained from all patients according to the principles of the Declaration of Helsinki.

TABLE I Results Obtained in the Two Groups on Blood Pressure, Glycemia, Glycated Hemoglobin, Plasma Sodium and Plasma Potassium

Variables	Month					
	0	3	6	12	18	24
Patients with Normoalbuminuria						
Systolic blood pressure (mm Hg)	160.0 (4.1)	150.0* (4.3)	145.0† (5.2)	135.5† (3.8)	129.5† (2.6)	128.5† (2.2)
Diastolic blood pressure (mm Hg)	95.5 (2.2)	91.1* (1.6)	88.0† (3.1)	83.5† (1.1)	81.5† (0.8)	81.5† (0.8)
Fasting blood glucose (mg/dl)	128.1 (5.3)	120.3 (4.6)	118.4 (3.9)	124.7 (5.2)	116.8 (3.4)	112.0 (4.7)
Postprandial blood glucose (mg/dl)	156.6 (7.7)	154.7 (4.8)	149.5 (6.3)	153.3 (5.1)	152.0 (4.3)	151.0 (3.6)
Glycated hemoglobin (%)	5.84 (0.54)	6.33 (0.48)	5.91 (0.44)	6.18 (0.34)	6.58 (0.23)	6.48 (0.19)
Plasma sodium (mEq/liter)	141.2 (1.0)	141.3 (0.8)	142.4 (0.9)	141.3 (0.8)	139.8 (0.4)	140.2 (0.5)
Plasma potassium (mEq/liter)	4.52 (0.10)	4.28 (0.09)	4.21 (0.09)	4.32 (0.12)	4.13* (0.11)	4.03† (0.04)
Patients with Microalbuminuria						
Systolic blood pressure (mm Hg)	181.5 (3.3)	168.5† (3.9)	159.0† (3.9)	151.0† (3.1)	142.5† (3.4)	129.5† (1.2)
Diastolic blood pressure (mm Hg)	99.0 (2.2)	93.0† (1.9)	89.5† (1.4)	85.5† (1.2)	84.0† (1.2)	79.5† (1.6)
Fasting blood glucose (mg/dl)	123.5 (6.1)	115.4 (6.1)	120.0 (4.4)	111.3 (3.0)	112.0 (3.6)	116.0 (3.4)
Postprandial blood glucose (mg/dl)	149.3 (5.7)	146.6 (7.3)	148.3 (3.5)	145.1 (4.2)	148.5 (3.6)	128.0 (14.5)
Glycated hemoglobin (%)	6.70 (0.17)	6.40 (0.26)	6.60 (0.23)	6.40 (0.28)	6.66 (0.17)	6.58 (0.15)
Plasma sodium (mEq/liter)	142.3 (0.9)	140.0 (0.6)	143.2 (0.9)	142.2 (1.0)	141.1 (0.7)	140.6 (0.5)
Plasma potassium (mEq/liter)	4.30 (0.07)	4.28 (0.11)	4.35 (0.08)	4.21 (0.11)	4.07 (0.09)	4.13 (0.09)

vs basal values * $p < 0.05$; † $p < 0.01$.
Values are mean ± standard deviation.

The patients had mildly increased arterial blood pressure: systolic blood pressure ranging between 150 and 180 mm Hg, diastolic blood pressure ranging between 90 and 105 mm Hg. They were given a diet with a fixed amount of protein (1 g/kg) and carbohydrate and a normal dietary intake of sodium; 11 of 21 were receiving treatment with oral hypoglycemic drugs (sulfonylureas). Patients were not included if there was any evidence of hepatic or gastrointestinal disease, marked dyslipidemia, renal or urinary tract diseases or cardiac insufficiency.

After a washout period of 15 days, patients were treated with indapamide (2.5 mg/day orally) and followed up for 24 months. At monthly intervals blood pressure was measured, every 3 months fasting and postprandial blood glucose, glycated hemoglobin (HbA_{1C}), plasma sodium and potassium were evaluated, and every 6 months AER, GFR and urinary IgG_4 were determined.

Blood pressure was measured with a standard mercury sphygmomanometer (cuff 25 × 12 cm). Measurements were performed 3 times after 10 minutes of rest in the supine position. Diastolic blood pressure was measured at the disappearance of Korotkoff sounds (phase V).

Serum sodium and potassium concentrations were measured by the Jaffe cromogen reaction. Glycemia was analyzed with the glucose-oxidase method with an autoanalyzer. HbA_{1C} was determined with microcolumn chromatography.

GFR was determined after a single intravenous injection of 100 of μCu ^{51}Cr-ethylene diaminetetraacetic acid (EDTA) (Sorin Biomedica, Saluggia, Italy) by studying the plasma radioactivity in venous blood samples taken from the other arm 90, 120, 150, 180, 210 and 240 minutes after the injection. The results were corrected according to the standard body surface area (1.73 m^2).[6] Values in control subjects were 115 ± 15.4 $ml \cdot min^{-1} \times 1.73\ m^2$.

Albuminuria was assayed by a method based on the competitive binding between ^{125}I-labeled and unlabeled albumin against antialbumin immunoglobulins coating plastic tubes. This procedure, which was developed in our laboratory, detects up to 25 ng of albumin per milliliter.[7]

A solid phase immunoenzymatic sandwich method was used to determine urinary IgG_4. This method was devised in our laboratory and used monoclonal antibody to human immunoglobulin subclasses indirectly bound to

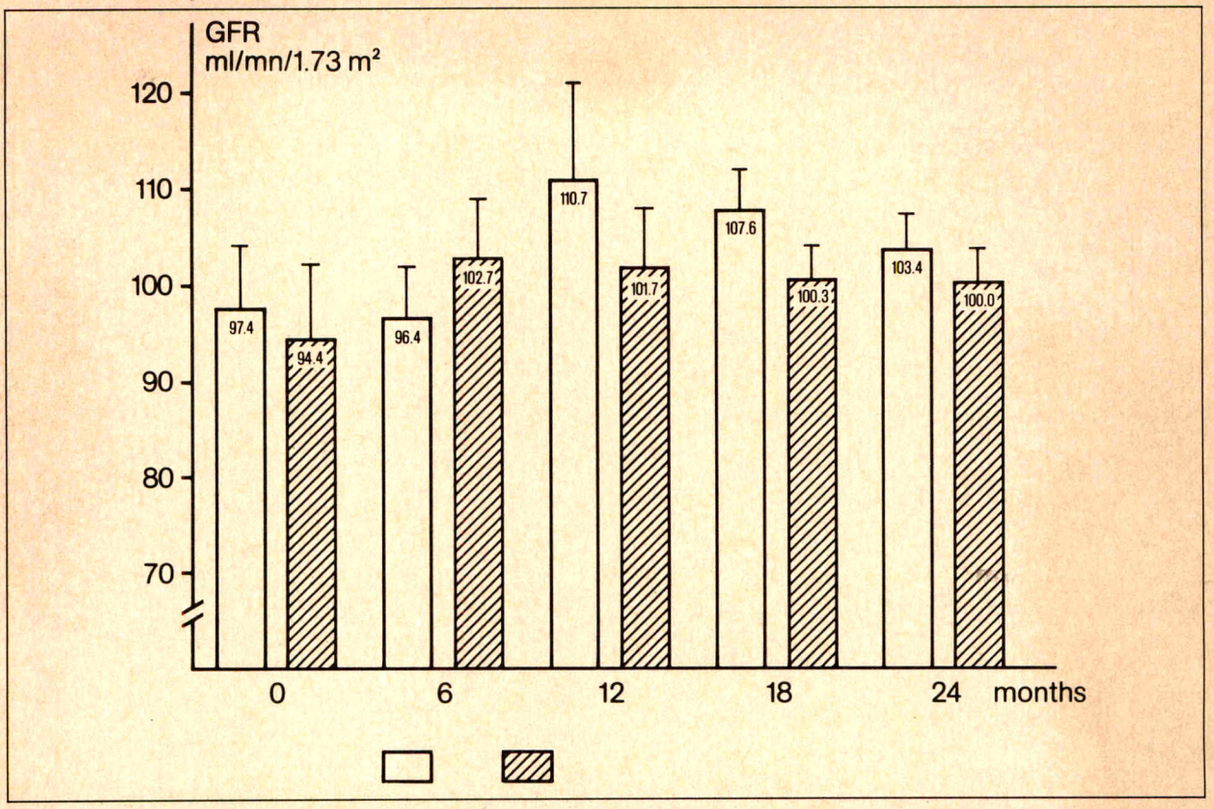


FIGURE 1. Glomerular filtration rate (GFR) in the lower limit of the normal range either in normoalbuminuric *(open bars)* or in microalbuminuric *(slashed bars)* patients at the beginning of the study. There was no significant variation throughout the observation period.

a solid matrix. The urinary human immunoglobulin subclass was identified from an enzyme-labeled antihuman immunoglobulin antibody. This assay can detect less than 1 ng/ml of IgG_4 (normal range 0.9 to 3.9 ng/ml).[8]

Urine samples were kept at −20°C until analysis, which was performed in random order within 2 months.

Results are expressed as mean ± standard deviation. The variations of quantitative variables with indapamide treatment were tested by a 2-way analysis of variance (group × time) with repeated measures, and by a 2-way analysis of variance (time × subject) without repetition of all the values obtained between 1 and 24 months; in the case of a significant time effect, the Newman-Keul's test for multiple comparisons was performed.

RESULTS

Results were obtained in 10 normoalbuminuric (group 1) and 10 microalbuminuric (group 2) patients.

Effects on blood pressure (Table I): After 3 months of therapy, systolic and diastolic blood pressures had decreased significantly ($p < 0.01$) and remained significantly reduced until month 24 ($p < 0.01$).

Effects on glucose tolerance (Table I): Indapamide had no statistically significant effect on mean blood glucose concentrations. There were no changes in mean fasting and postprandial blood glucose, and glycated hemoglobin remained unchanged.

Effects on sodium and potassium balance (Table I): Plasma sodium concentrations were similar in both groups and no significant change was observed in this study. Indapamide did not lower serum potassium concentrations in microalbuminuric patients (group 2) but a statistically significant decrease in mean serum potassium concentration occurred in normoalbuminuric patients (group 1), from 4.52 to 4.13 mEq/liter at month 18 ($p < 0.05$) and to 4.03 mEq/liter at month 24 ($p < 0.01$).

Effect on renal function: Basal GFR was slightly reduced in group 2 and in the lower limit of the normal range in group 1; it did not show any significant difference throughout the study in either group (Fig. 1). There was a constant, significant reduction in the high albumin excretion rate in group 2 (Fig. 2). In normoalbuminuric patients, AER showed no variation throughout the observation period.

As expected, basal IgG_4 excretion was elevated in group 2 compared with that in group 1 (20.77 ± 2.25 vs 3.30 ± 0.43 ng/ml). At the end of the study, a significant reduction was achieved in the former group without reaching normal values (Fig. 3). Unfortunately, no relationship was found between blood pressure, AER and IgG_4 and between AER and IgG_4 excretion.

DISCUSSION

After some 15 years of disease, one-third of patients with insulin-dependent diabetes develop the clinical syndrome of diabetic nephropathy: persistent proteinuria (AER >300 mg/24 hours), a decline in the GFR and an increase in blood pressure.[9] In patients with noninsulin-

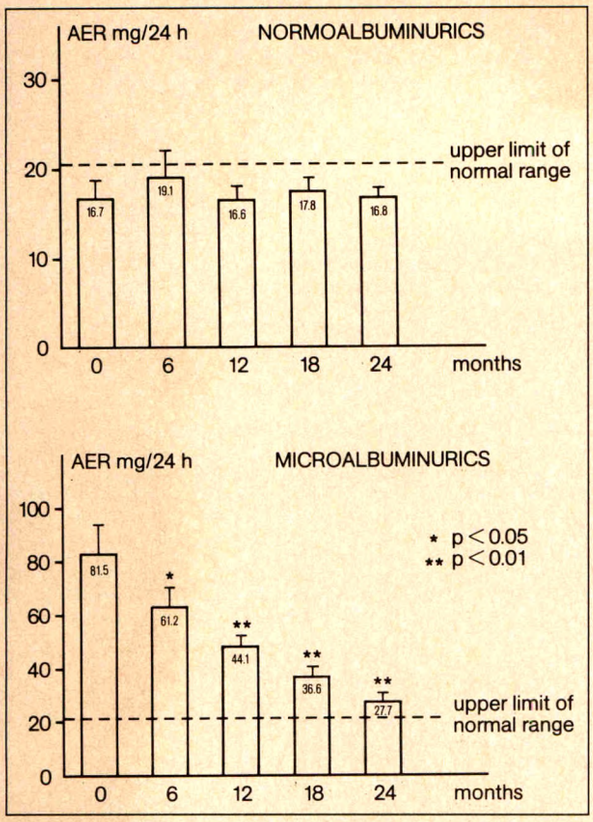


FIGURE 2. Evolution of albumin excretion rate (AER) in normoalbuminuric and microalbuminuric patients.

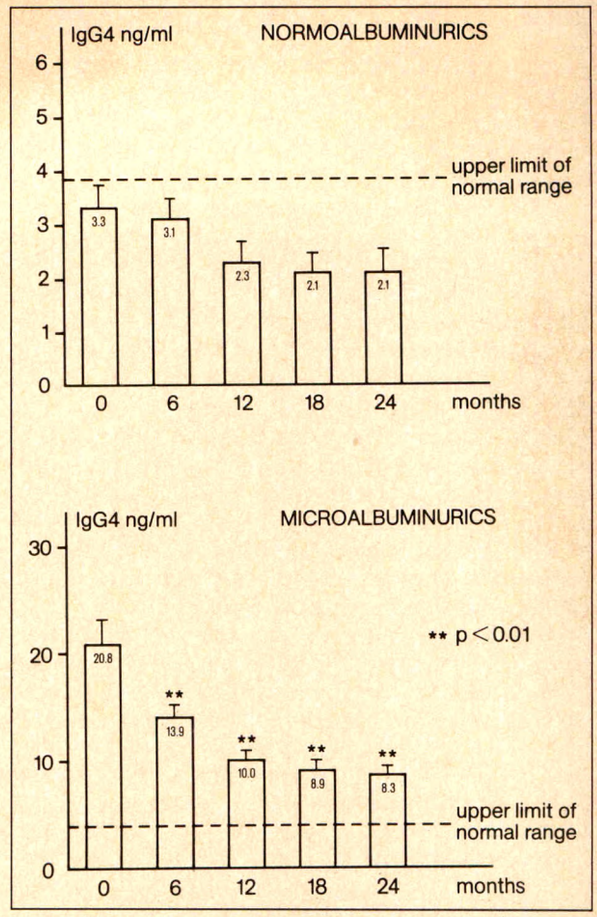


FIGURE 3. Evolution of urinary IgG_4 in normoalbuminuric and microalbuminuric patients.

dependent diabetes the incidence of nephropathy is much lower (5%), but, because of the high numbers of noninsulin-dependent diabetics in the general population, a similar number of these patients reach the end stage of renal failure.[10,11] Both experimental[12] and clinical[13] studies emphasize the importance of systemic arterial hypertension in the progression of diabetic nephropathy in either type of diabetes.

In our study, systolic blood pressure was significantly higher in microalbuminuric than in normoalbuminuric patients (181.5 ± 3.3 vs 160.0 ± 4.1 mm Hg, $p < 0.001$), but there was no difference in diastolic blood pressure. These results are not in complete agreement with those previously observed in insulin-dependent diabetics in whom both systolic and diastolic blood pressures have been found to be significantly higher at the onset of incipient nephropathy.[14] This result is probably due to the fact that approximately 20% of noninsulin-dependent diabetics are hypertensive before the diagnosis of the disease,[15] and there are various pathogenetic mechanisms in hypertension including hyperinsulinemia and obesity.

Extensive prospective studies have suggested that diabetic patients with AER ranging between 30 and 300 mg/24 hours (so-called "microalbuminuria") present a 20-fold increased risk of developing clinical nephropathy compared with patients with AER below this level.[16–19] The risk may be reduced by continuous subcutaneous insulin infusion or by careful antihypertensive treatment.[20]

Albuminuria is currently the most reliable parameter to monitor the different stages of diabetic nephropathy.[19] Nevertheless, albumin has a relatively small molecular weight, and small amounts of it may be found in the urine as a result of factors such as physical exercise, orthostatism, urinary infections, water loading and hypertension (albumin shows wide variability: approximately 30 and 45%[21]). To overcome this problem, some investigators have focused attention on subclasses of immunoglobulin G, medium-sized proteins of similar molecular weight but with different electrostatic charges; among these subclasses, IgG_4 is the only anionic immunoglobulin G.[22–24]

We have found significantly higher excretion of urinary IgG_4 in microalbuminuric than in normoalbuminuric patients and in control subjects. After 6 months of treatment, there was a significant decrease in either AER or IgG_4 excretion which persisted during medium-term follow-up.

Our results suggest that in noninsulin-dependent patients with microalbuminuria, excretion of both small and medium-sized anionic proteins is increased. This indicates an underlying charge-selectivity alteration of the glomerular wall. The evidence for a relatively rapid decrease in the excretion of such proteins after antihypertensive treatment appears to be related to the reduction in

systemic arterial pressure. Moreover, the reduction in albumin and IgG_4 excretion was not accompanied by a decrease in GFR, which suggests that other mechanisms are involved. Since the kidney vasculature of diabetic patients exhibits marked vasodilation, it seems likely that even slight reductions in systemic arterial pressure would reduce glomerular capillary hydraulic pressure, as shown in experimental studies in rats, and thereby prevent the subsequent development of glomerular injury.[25]

Different studies have shown that microalbuminuria is enhanced by poor glycemic control[26–28] and lowered by restriction of dietary protein intake.[29–31] In our microalbuminuric group, however, blood glucose control did not show any significant variation during the study period (Table I) and the diet was not changed with respect to protein intake. Urinary urea excretion, which can be used as an estimate of protein intake, was stable during the period of observation (basal: 246 ± 84; 12 months: 271 ± 93; 24 months: 253 ± 88 mol/24 hours). Therefore, we believe that neither metabolic control nor protein intake had any significant influence on our results.

We conclude that in the early phase of diabetic nephropathy a charge-selectivity impairment is responsible for the urinary loss of anionic proteins. Nevertheless, the possible role of tubular reabsorption requires clarification.

Antihypertensive treatment results in a decrease in urinary protein excretion in patients with "incipient" diabetic nephropathy. Whether these changes will also help to delay the course of progressive renal failure cannot be evaluated from our study and has yet to be established from longer periods of observation.

REFERENCES

1. Shimamatsu K, Onoyama K, Harada A, Kumagai H, Hirakata H, Miishima C, Inenaga T, Fujimi S, Fujishima M, Omae T. Effect of blood pressure on the progressive rate of renal impairment in chronic glomerulonephritis. *J Clin Hypertens 1985;3:239–244.*

2. Mogensen C. Long-term antihypertensive treatment inhibiting progression of diabetic nephropathy. *Br Med J 1982;1:2–7.*

3. Parving H-H, Andersen AR, Smidt UM, Svendsen PAA. Early aggressive antihypertensive treatment reduces rate of decline in kidney function in diabetic nephropathy. *Lancet 1983;1:1175–1179.*

4. Klein R, Klein BEK, Moss SE, Demets DL. Blood pressure and hypertension in diabetes. *Am J Epidemiol 1985;122:75–89.*

5. Hommel E, Mathiesen E, Edsberg B, Boehnsen M, Parving H-H. Acute reduction of arterial blood pressure reduces urinary albumin excretion in type 1 (insulin-dependent) diabetic patients with incipient nephropathy. *Diabetologia 1986;29:211–215.*

6. Granerus G, Aurell M. Reference values for ^{51}Cr-EDTA clearance as measure of glomerular filtration rate. *Scand J Clin Lab Invest 1981;41:611–616.*

7. Di Mario U, Pietravalle P, Napoli A, Morano S, Mancuso M, Gambardella S, Andreani D. A sensitive routine assay for urinary albumin based on the competitive binding to anti-albumin antibodies in solid phase. *Horm Metabol Res 1986;18:689–692.*

8. Morano S, Cancelli A, Mancuso M, Sensi M, Negri M, Gambardella S, Di Mario U. Sensitive immunoenzymatic assay for urinary immunoglobulin subclasses of different pH: its significance in diabetic patients. *Diabetes Res 1987;6:181–185.*

9. Andersen AR, Christiansen LS, Andersen JK, Kreiner S, Deckert T. Diabetic nephropathy in type 1 (insulin dependent) diabetes: an epidemiological study. *Diabetologia 1983;25:496–501.*

10. Rettig B, Teutsch SM. The incidence of end-stage renal disease in type 1 and type 2 diabetes mellitus. *Diabetic Nephrop 1983;3:26–27.*

11. Nelson RG, Newman JM, Knowler WC, Sievers ML, Kunzelman CL, Pettitt DJ, Moffett CD, Teutsch SM, Bennett PH. Incidence of end-stage renal disease in type 2 (non insulin-dependent) diabetes mellitus in Pima Indians. *Diabetologia 1988;31:730–736.*

12. Anderson S, Meyer TW, Rennke HG, Brenner BM. Control of glomerular hypertension limits glomerular injury in rats with reduced renal mass. *J Clin Invest 1985;76:612–619.*

13. Ritz E, Hasslacher C, Tshope W, Koch M, Mann JFE. Hypertension in diabetes. *Contrib Nephrol 1987;54:77–85.*

14. Jensen T, Borch-Johnsen K, Deckert T. Changes in blood pressure and renal function in patients with type 1 (insulin-dependent) diabetes mellitus prior to clinical diabetic nephropathy. *Diabetes Res 1987;4:159–162.*

15. Fabre J, Balant LP, Dajerp G, Fox HM, Vernet AT. The kidney in maturity onset diabetes mellitus. A clinical study of 510 patients. *Kidney Int 1982;21:730–734.*

16. Viberti GC, Hill RD, Jarrett RJ. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. *Lancet 1982;1:1430–1432.*

17. Mathiesen ER, Oxenboll K, Johansen PAO, Svendsen PA, Deckert T. Incipient nephropathy in type 1 (insulin-dependent) diabetes. *Diabetologia 1984;26:406–410.*

18. Mogensen CE, Christensen CK. Predicting diabetic nephropathy in insulin-dependent diabetes. *N Engl J Med 1984;311:89–93.*

19. Parving HH, Oxenboll B, Svendsen PAa, Christiansen JS, Andersen AR. Early detection of patients at risk of developing diabetic nephropathy. A longitudinal study of urinary albumin excretion. *Acta Endocrinol 1982;100:550–555.*

20. KROC Collaborative Study Group. Blood glucose control and the evolution of diabetic retinopathy and microalbuminuria. *N Engl J Med 1984;311:365–372.*

21. Mathiesen ER, Oxenboll B, Johansen K, Svendsen PAa, Deckert T. Incipient nephropathy in type 1 (insulin-dependent) diabetes. *Diabetologia 1984;26:406–410.*

22. Morano S, Cancelli A, Bacci S, Frontoni S, Napoli A, Fallucca F, Gambardella S, Di Mario U. The selective elimination of anionic immunoglobulins as a parameter of kidney damage in diabetics and diabetic pregnancy. *J Diab Complications 1988;41:24–28.*

23. Deckert T, Feldt-Rasmussen B, Pjuzup R, Deckert M. Glomerular size and charge selectivity in insulin-dependent diabetes mellitus. *Kidney Int 1988;33:21–26.*

24. Nakamura Y, Myers BD. Charge selectivity of proteinuria in diabetic glomerulopathy. *Diabetes 1988;37:1202–1211.*

25. Zatz R, Dunn BR, Meyer TW, Anderson S, Rennke HG, Brenner BM. Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. *J Clin Invest 1986;77:1925–1930.*

26. Mathiesen ER, Oxenboll B, Johansen K. Incipient nephropathy in type 1 (insulin-dependent) diabetes. *Diabetologia 1984;26:406–410.*

27. Mogensen CE, Christiansen CK. Predicting diabetic nephropathy in insulin-dependent patients. *N Engl J Med 1984;311:89–93.*

28. Kern TS, Engerman RL. Urinary protein excretion rates in experimentally diabetic dogs and experimentally glactosaemic dogs. *Diabetologia 1988;31:928–932.*

29. Kupin WC, Cortes P, Dommler F, Kilates MC, Lewin NW. Effect on renal function of change from high to moderate protein intake in type 1 diabetic patients. *Diabetes 1987;36:73–79.*

30. Wiseman MJ, Bognetti E, Dodds R, Keen H, Viberti GC. Changes in renal function in response to protein restricted diet in type 1 (insulin-dependent) diabetic patients. *Diabetologia 1987;30:154–159.*

31. Cohen DL, Dodds RA, Biberti GC. Effect of protein restriction in insulin-dependent diabetics at risk of nephropathy. *Br Med J 1987;294:795–798.*

Long-Term Diuretic Therapy and Renal Function in Essential Arterial Hypertension

Jose M. Alcazar, MD, Jose L. Rodicio, MD, and Luis M. Ruilope, MD

One of the main objectives of antihypertensive therapy is to preserve renal function from the deleterious effects of elevated blood pressure. Diuretics alone or in combination are effective for the treatment of arterial hypertension. Nevertheless, their use is accompanied by unwanted biochemical side effects, which have been attributed to their renal effects.

During the last 10 years a group of 211 patients, diagnosed as having essential hypertension, were followed up. During the follow-up, they received a stepped-care therapeutic regimen consisting of nonpharmacologic measures (group 1), hydrochlorothiazide and amiloride (group 2), propranolol (group 3) and, if necessary, hydralazine (group 4).

During the study, blood pressure remained within comparable, well-controlled levels in the 4 groups of patients. A progressive elevation of the levels of total serum cholesterol and glucose was observed in every group. The elevation attained statistical significance ($p < 0.01$) after 4 years of therapy in those groups receiving the diuretic alone or in combination. Nevertheless, after 8 years of follow-up, the increment observed in these 2 parameters did not differ when patients in group 1 were compared with those in the remaining groups, indicating that thiazide diuretics could contribute to the earlier appearance of forthcoming events. Serum potassium levels were significantly lower ($p < 0.01$) in groups 2 and 3 than in group 1.

At the same time, we have observed the progressive appearance of clinically relevant proteinuria in 15.2% of patients, and the range of protein excretion ranged from 350 to 3,700 mg/24 hours. The appearance of proteinuria did not depend on the lack of control of blood pressure, nor on the different therapeutic requirements but was accompanied by a progressive decrease in creatinine clearance.

The consequences of the renal effects of diuretics are of great importance during long-term therapy. The present results indicate that diuretics preempt the appearance of a forthcoming increase in serum glucose and cholesterol, and lessen the clinical relevance of these events. On the other hand, diuretic therapy alone or in combination does not seem to fully protect the kidney from the deleterious effects of arterial hypertension.

(Am J Cardiol 1990;65:51H–54H)

Oral diuretics are among the most widely used drugs in clinical practice today. Use of these drugs has greatly contributed to the observed reduction in morbidity and mortality in arterial hypertension, which has been brought about mainly by the prevention of stroke and congestive heart failure.[1] Their influence on the incidence of coronary artery disease has, nevertheless, not been shown to be beneficial in any clinical trial. This fact has been attributed, at least partly, to the biochemical side effects of diuretic therapy,[2] which are mainly attributable to their pharmacologic action on the kidney.[3]

The relationship of hypertension to progressive renal dysfunction remains a matter of debate. A clear improvement of renal function or an arrest in its deterioration during treatment has been shown in malignant hypertension.[4–6] Other studies have shown, however, that renal impairment may develop despite an excellent control of blood pressure with different therapeutic regimens including diuretics.[7–10]

The aim of this report is to review briefly our experience with the renal effects of diuretic therapy alone or in combination during the long-term treatment of a group of 211 patients diagnosed as having mild to moderate essential hypertension and followed up for 10 years. Patients were included in a stepped-care therapeutic regimen according to the following successive steps: nonpharmacologic measures (group 1), and a diuretic (hydrochlorothiazide and amiloride) (group 2) to which a β blocker (propranolol) (group 3) was added if necessary. Hydralazine was used as the third drug (group 4) if blood pressure control was unsatisfactory.

BIOCHEMICAL SIDE EFFECTS OF DIURETIC THERAPY

The likely development of most of the more common complications of diuretic use appears to be related to the intrinsic activity of these drugs and depends on the dose and duration of treatment.[3] The most relevant adverse effects are hyperuricemia and the impairment of glucose tolerance, which is related to hypokalemia and hyperlipi-

From the Hypertensive Unit, Department of Nephrology, 12 de Octubre Hospital, Madrid, Spain.

Address for reprints: Luis M. Ruilope, MD, Hypertensive Unit, Department of Nephrology, 12 de Octubre Hospital, Carretera de Andalucia Km 5.400, 28041 Madrid, Spain.

TABLE I Serum Potassium Levels (mmol/liter) in Groups 1 to 4

		Year								
	Baseline	1	2	3	4	5	6	7	8	9
Group 1 (n = 39)	4.1 ± 0.4	4.2 ± 0.3	4.1 ± 0.4	4.2 ± 0.4	4.3 ± 0.4*	4.3 ± 0.4*	4.3 ± 0.4*	4.4 ± 0.4*	4.4 ± 0.3*	4.4 ± 0.3*
Group 2 (n = 96)	4.1 ± 0.4	4.06 ± 0.4	4.1 ± 0.3	4.05 ± 0.4	4.02 ± 0.4	4.0 ± 0.4	4.1 ± 0.4	4.1 ± 0.4	4.1 ± 0.4	4.1 ± 0.3
Group 3 (n = 50)	3.95 ± 0.5	4.2 ± 0.5	4.1 ± 0.5	4.1 ± 0.5	4.1 ± 0.5	4.1 ± 0.5	4.1 ± 0.4	4.2 ± 0.4	4.3 ± 0.5	4.2 ± 0.4
Group 4 (n = 26)	4.2 ± 0.6	3.9 ± 0.6	4.1 ± 0.5	4.2 ± 0.5	4.05 ± 0.4	4.06 ± 0.6	4.1 ± 0.5	4.1 ± 0.4	4.1 ± 0.5	4.1 ± 0.4

* Significant ($p < 0.01$) difference between groups.
Values are mean ± standard deviation.

TABLE II Serum Glucose Values (mmol/liter) in Groups 1 to 4

		Year								
	Baseline	1	2	3	4	5	6	7	8	9
Group 1 (n = 39)	5.2 ± 0.6	5.2 ± 0.7	5.2 ± 0.7	5.2 ± 0.6	5.0 ± 0.7	5.4 ± 0.7	5.7 ± 1.8†	5.6 ± 1.0†	5.7 ± 0.9†	5.7 ± 0.8†
Group 2 (n = 96)	5.3 ± 0.9	5.4 ± 1.0	5.4 ± 1.6	5.4 ± 0.9	5.5 ± 0.9*	5.6 ± 1.1*	5.8 ± 0.8*	5.7 ± 0.9†	5.9 ± 1.1†	5.8 ± 0.8†
Group 3 (n = 50)	5.6 ± 1.3	5.6 ± 0.8	5.6 ± 1.3	5.8 ± 1.0	5.9 ± 1.3*	6.2 ± 1.8†	5.9 ± 1.1*	5.9 ± 1.0†	5.8 ± 0.8†	5.9 ± 0.9
Group 4 (n = 26)	5.4 ± 1.2	5.7 ± 1.1	5.7 ± 1.4	5.9 ± 1.4	6.0 ± 1.3†	6.1 ± 1.5†	6.0 ± 1.1†	6.1 ± 1.0†	6.2 ± 0.9†	6.1 ± 1.1†

* Significant ($p < 0.05$) difference from baseline.
† Significant ($p < 0.01$) difference from baseline.
Values are mean ± standard deviation.

TABLE III Serum Cholesterol Values (mmol/liter) in Groups 1 to 4

		Year								
	Baseline	1	2	3	4	5	6	7	8	9
Group 1 (n = 39)	5.25 ± 1.0	5.43 ± 1.0	5.48 ± 0.6	5.61 ± 1.4	5.74 ± 1.0	6.03 ± 1.8*	6.08 ± 1.8†	6.10 ± 1.8†	6.39 ± 1.3†	6.21 ± 0.9†
Group 2 (n = 96)	5.46 ± 1.8	5.61 ± 1.0	5.48 ± 1.1	5.69 ± 1.1	5.92 ± 1.2†	5.92 ± 1.1†	6.0 ± 1.2†	6.0 ± 1.3†	5.95 ± 1.3†	6.03 ± 0.9†
Group 3 (n = 50)	5.48 ± 1.2	5.30 ± 1.0	5.28 ± 1.0	5.69 ± 1.0	6.08 ± 1.4†	5.9 ± 1.1†	6.0 ± 1.2†	6.21 ± 0.9†	6.39 ± 0.9†	6.28 ± 0.9†
Group 4 (n = 26)	5.30 ± 1.0	5.46 ± 0.7	5.51 ± 0.6	5.4 ± 0.8	5.64 ± 0.9	5.79 ± 1.0*	5.95 ± 1.2†	5.79 ± 1.1*	5.9 ± 1.1†	5.95 ± 0.7†

* Significant ($p < 0.05$) difference from baseline.
† Significant ($p < 0.01$) difference from baseline.
Values are mean ± standard deviation.

demia. Hyperuricemia is present in as many as 30% of untreated hypertensive patients, and this percentage can double with the use of a thiazide diuretic.[11,12] There is a general agreement that in the absence of clinical manifestations related to uric acid deposition, hyperuricemia does not need to be treated.

In a previous publication by our group,[13] we described the unwanted biochemical side effects that appeared in this same group of patients after 5 years of follow-up. Then, groups 2, 3 and 4, in which diuretics were used alone or in combination with a β blocker and a vasodilator, had a significant increase in serum glucose and total cholesterol that was not seen in the group controlled with nonpharmacologic methods. Patients taking the diuretics alone or in combination also had significantly lower levels of serum postassium.

Hypokalemia is the most serious adverse effect of long-term diuretic therapy. The values of serum potassium in the 4 groups of patients were not different at the beginning of the study (Table I). During the follow-up, patients did not show any significant variation in kalemia. This differs from the study of Morgan and Davidson[14] who reported hypokalemia when only a thiazide diuretic was used.

Impairment of glucose tolerance has also been described with the use of thiazide diuretics. It appears to be closely related to diuretic-induced hypokalemia, which decreases insulin secretion.[15] In our patients, a significant

increase in serum glucose was already seen in the fourth year of diuretic therapy in the 3 groups in which this drug was used (Table II). Unexpectedly, a significant increase in serum glucose levels was observed in group 1 from the sixth year of follow-up and thereafter. The glucose levels in group 1 were not significantly different from those observed in the other 3 groups at the end of the follow-up. These results seem to indicate that when considering serum glucose levels, diuretic therapy appears to preempt a forthcoming event.

The effect of diuretic therapy on the lipid profile of hypertensive patients is characterized by an increase in total cholesterol, triglycerides, and very low density lipoprotein cholesterol levels.[16] After 4 years of diuretic therapy, these patients had a significant increase in total serum cholesterol, but a progressive decrease in triglycerides was observed in the 4 groups.[13] This pattern of triglycerides has been maintained throughout the study. The interpretation of this finding is not easy to explain. The Oslo Study[17] found no change in serum triglyceride levels during a follow-up of 5 years with the same diuretic combination that was used in this study. It is possible that the type of diuretic used could have influenced the different behavior of serum triglycerides observed. A change in dietary habits could also explain this decrease.

The elevation in total cholesterol levels was maintained during the long-term follow-up in groups 2, 3 and 4 (Table III). The patients in group 1, who did not receive drugs, also had a significant increase in total serum cholesterol from the sixth year of treatment. As in the case of serum glucose, the levels of total cholesterol in group 1 were not different when compared with the groups that received the diuretic. These results point to the existence of a progressive increase in total cholesterol in the hypertensive population independently of the use of antihypertensive medication. Diuretic therapy may then preempt a forthcoming elevation of cholesterol. The analysis of our data is in agreement with previous reports[18] in which the increase was more marked in postmenopausal women.

ARTERIAL HYPERTENSION AND PROGRESSIVE RENAL DYSFUNCTION

The reduction of blood pressure does not always slow the progression of renal damage. Since the initial work of Perera,[19] it is known that untreated arterial hypertension leads to the development of renal vascular damage characterized by the appearance of proteinuria and renal insufficiency. Arterial hypertension is known to damage the kidney through 2 different mechanisms. One is vasoconstriction and intrarenal vascular sclerosis; the second is the transmission of the elevated systemic pressure to the glomeruli, leading to increased glomerular pressure and flow.[20]

In our patients, we have observed the progressive development of overt proteinuria (>300 mg/day), attaining a 17.5% incidence by the end of the follow-up. The development of proteinuria did not depend on a lack of control of blood pressure or on different therapeutic requirements.[21] The groups of patients presenting with proteinuria at the end of the study had a progressive increase in serum creatinine accompanied by a decrease in creatinine clearance (Table IV).

TABLE IV Serum Creatinine Levels (μmol/liter) and Creatinine Clearance (ml/min) in Patients

	Serum Creatinine		Creatinine Clearance	
	Baseline	End of Study	Baseline	End of Study
Patients developing proteinuria	97 ± 44	124 ± 35*	88 ± 30	71 ± 28*
Patients not developing proteinuria	88 ± 27	88 ± 18	87 ± 25	82 ± 21

* Significant ($p < 0.01$) difference from baseline.
Values are mean ± standard deviation.

The interpretation of these results is difficult. The development of proteinuria has been described in spontaneously hypertensive rats as genetic.[22] It is also possible that the type of antihypertensive drug used causes a certain degree of glomerular damage. In fact, the use of a similar therapeutic regimen has been proved not to be useful in the prevention of glomerular damage secondary to the maintenance of an increased intraglomerular capillary pressure.[23]

CONCLUSION

In summary, our results indicate that diuretic therapy alone or in combination induces an increase in serum glucose and total cholesterol levels that is not as clinically relevant as previously thought. On the other hand, although a prevention of progressive renal dysfunction exists when compared with untreated patients, this therapeutic regimen does not seem to fully protect renal function in hypertensive patients.

REFERENCES

1. MacMahon SW, Cutler JA, Furberg CD, Payne GH. The effects of drug treatment for hypertension on morbidity and mortality from cardiovascular disease. A review of randomized controlled trials. *Prog Cardiovasc Dis 1986; 29:suppl 1:99–118.*

2. Hansson L. What are we really achieving with long-term drug therapy. *Am J Hypertens 1988;1:414–420.*

3. Kaplan NM. In: Clinical Hypertension. *Baltimore: Williams & Wilkins. 1986; 192.*

4. Dustan HP, Scheneckloth RE, Corcoran AC, Page IH. The effectiveness of long-term treatment of malignant hypertension. *Circulation 1958;18:644–651.*

5. Gudbrandsson T, Hansson L, Helitz H, Andren L. Malignant hypertension—improving prognosis in a rare disease. *Acta Med Scand 1979;206:495–499.*

6. Alcazar JM, Sanz J, Ruilope LM, Rodicio JL. Hipertension arterial maligna. In: Rodicio JL, Romero JC, eds. Tratado de Hipertension. *Barcelona: Salvat Editores, 1986;329–346.*

7. Macger JH, Unger AM, Richardson DW. Changes in renal function associated with drug or placebo therapy of human hypertension. *Am J Med 1964;36: 795–804.*

8. Mitchell HC, Graham RM, Pettinger WA. Renal function during long-term treatment of hypertension with minoxidil: comparison of benign and malignant hypertension. *Ann Intern Med 1980;93:676–681.*

9. Ljungman S, Aurell M, Hartford M, Wikstrand J, Berglund G. Renal function before and after withdrawal of long-term antihypertensive treatment in primary hypertension. *Drugs 1988;35:suppl 5:55–58.*

10. Rodicio JL, Ruilope LM. The role of antihypertensive therapy in the progression of chronic renal failure. In: Hansson L, ed. Hypertension Annual. *London: Gower Academic Journals, 1988;47–58.*

11. Breckenridge A. Hypertension and hyperuricemia. *Lancet 1966;115–120.*

12. Alcazar JM, Ruilope LM, Ladron De Guevara P, Barrientos A, Gutierrez Millet V, Bello I, Rodicio JL. Hiperuricemia e hipertension arterial esencial. *Nefrologia 1982;II:145–150.*
13. Rodicio JL, Alcazar JM, Nieto J, Miranda B, Ruilope LM. Metabolic effects of long-term diuretic treatment. In: Andreucci VE, del Canton A, eds. Diuretics: Basic, Pharmacological and Clinical Aspects. *Boston: Martinus Nijhoff Publishing, 1987;231–236.*
14. Morgan DB, Davidson C. Hypokalemia and diuretics: an analysis of publication. *Br Med J 1980;280:905–910.*
15. Bloomgardan ZT, Ginsberg-Fellner F, Rayfield EJ, Brookman J, Brown WV. Elevated hemoglobin Alc and low-density lipoprotein cholesterol levels in thiazide-treated diabetic patients. *Am J Med 1984;77:823–827.*
16. Ames RP. Antihypertensive drugs and lipid profiles. *Am J Hypertens 1988;1:421–427.*
17. Helgeland A. Treatment of mild hypertension: a five year controlled drug trial. *Am J Med 1980;69:725–730.*
18. Boehringer K, Weidmann P, Mordasini R, Schiffl H, Bachmann C, Riesen W. Menopause dependent plasma lipoprotein alterations in diuretic treated women. *Ann Intern Med 1982;97:206–209.*
19. Perera GA. Hypertensive vascular disease: description and natural history. *J Chron Dis 1955;1:33–45.*
20. Baldwin DS, Neugarten J. Blood pressure control and progression of renal insufficiency. In: Mitch WE, Brenner BM, Stein JH, eds. The Progressive Nature of Renal Disease. *Edinburgh: Churchill Livingstone, 1986;81–110.*
21. Ruilope LM, Miranda B, Oliet A, Alcazar JM, Bachiller A, Rodicio JL. Does an adequate control of blood pressure protect the kidney in essential hypertension (abstr). *J Hypertens 1988;6:suppl:744.*
22. Feld LG, Vanliew JB, Bretjens JR, Boylan JW. Renal lesions and proteinuria in the spontaneously hypertensive rat made normotensive by treatment. *Kidney Int 1981;20:606–614.*
23. Raij L. Role of hypertension in progressive glomerular injury in glomerulonephritis. *Hypertension 1986;8:suppl 1:130–133.*

Diuretics and Transmembrane Ionic Exchanges: Structure-Activity Relations and Clinical Applications

Javier Diez, MD

The study of membrane ion transport has facilitated the discovery of potent and quite specific inhibitory drugs. Some of these compounds are therapeutic agents acting on basic transport mechanisms as in the case of the cardiac glycosides on the myocardial sodium ion (Na^+), potassium ion (K^+) pump, and the loop diuretics on the renal Na^+, K^+, chloride (Cl^-) co-transport system. The development of inhibitors for other transport systems such as Na^+/hydrogen ion (H^+), Na^+/calcium ion (Ca^{2+}) and bicarbonate (HCO_3^-)/Cl^- exchangers requires the screening of a large number of molecules. For several reasons, the human red blood cell is one of the best models for screening the effect of drugs on ion transport mechanisms. The use of human red cells for pharmacologic studies of ion transport has increased the understanding of the structure-activity relations of diuretics. For in stance, loop diuretics that are chemically neutral were considered for many years as drugs that act similarly to classic acid loop diuretics. They are now considered as potent inhibitors of HCO_3^-/Cl^- anion exchange. A brief summary of the more recent results is given together with the perspectives of new fundamental and therapeutic applications of these compounds.

(Am J Cardiol 1990;65:55H–57H)

From the Department of Medicine, University of Zaragoza, Zaragoza, Spain.

Address for reprints: Javier Diez, MD, Department of Medicine, Facultad de Medicina, C/ Domingo Miral S/N, 51009 Zaragoza, Spain.

Classically, hemodynamic and metabolic effects of diuretics on the kidney were considered as the primary mechanisms of action of these drugs. However, the mechanism of action of most diuretics is now considered to be a direct effect of the drug on the tubular reabsorption of salt and water. More specifically, diuretics inhibit the transport processes that control ion reabsorption at each segment of the nephron.[1]

Recent experiments on both renal and nonrenal tissue have provided new insights into the molecular mechanisms of inhibition of ion transport by diuretics. This report briefly reviews recent pharmacologic studies together with their potential applications.

STRUCTURE-ACTIVITY RELATIONS

The ion transport systems of human red cell membranes are pharmacologically similar to those of other cells. In addition, correlations with chemical or physical properties of the cell membranes are facilitated by the great amount of information accumulated in the last few years concerning structural and functional properties of the red cell membrane. These and other reasons account for the fact that the human red blood cell is now widely used for screening the effect of drugs on ion transport mechanisms.[2]

From these studies it is established that the diuretics that inhibit ionic transport exchange can be divided into 3 groups: those acting at anion translocating sites, those acting at cation translocating sites, and those acting at nontranslocating sites.

Diuretics acting at anion translocating sites: The classic representatives of this group are the loop diuretics of the sulfamoylbenzoic family (furosemide, bumetanide and piretanide) and those of the (aryloxy) acetic acid family (ethacrinic acid and indacrinone). Their mechanism of action involves a competition of the $R\text{-}COO^-$ group with chloride for a common receptor site on different chloride (Cl^-) transport systems.[3] This is the situation with the sodium ion (Na^+), potassium ion (K^+), Cl^- co-transport system that exists in human red cells and which shares similar properties with the co-transport system catalyzing luminal Na^+ reabsorption at the thick ascending limb of Henle's loop.[4] Indeed, good correlations were found between saluretic activity of loop diuretics and inhibition of the Na^+, K^+, Cl^- co-transport system in erythrocytes.[5]

Diuretics acting at cation translocating sites: Amiloride is the main representative of this group of transport inhibitors. This compound has a guanidine group that is positively charged at physiologic pH and can therefore

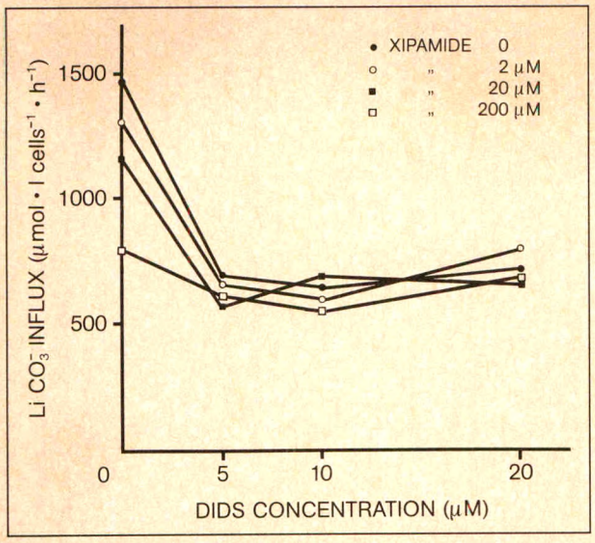


FIGURE 1. The effect of different concentrations of xipamide on the inhibition of the erythrocyte (HCO_3^-/Cl^-) anion exchanger by 4,4′-diisothiocyano-2,2′-stilbene-disulfonic acid (DIDS). No interaction was observed between xipamide and DIDS. Similar results were observed in 3 other experiments. (The activity of the anion exchanger was evaluated by measuring the DIDS-sensitive lithium carbonate ($LiCO_3^-$) influx in fresh erythrocytes incubated into a medium containing Li_2CO_3.)

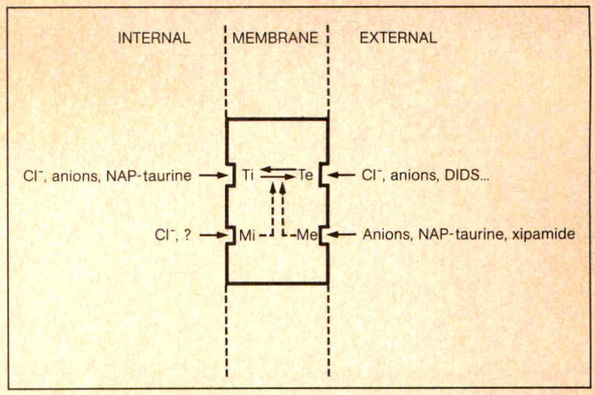


FIGURE 3. Representation of the site of inhibition of the erythrocyte HCO_3^-/Cl^- anion exchanger by each inhibitor. Xipamide might act at a modifying site located at the external surface of the membrane. Me = external modifying site; Mi = internal modifying site; Te = external translocating site; Ti = internal translocating site.

interact with the Na^+ sites of different carriers, as, e.g., the Na^+/hydrogen ion (H^+) exchange system.[6]

Different findings are consistent with the presence of an amiloride-sensitive Na^+/H^+ exchange system in human red cells.[7] Evidence suggests that this system, present in red blood cells, is the amiloride-sensitive Na^+/H^+ exchange found in renal microvillus membrane vesicles.[8]

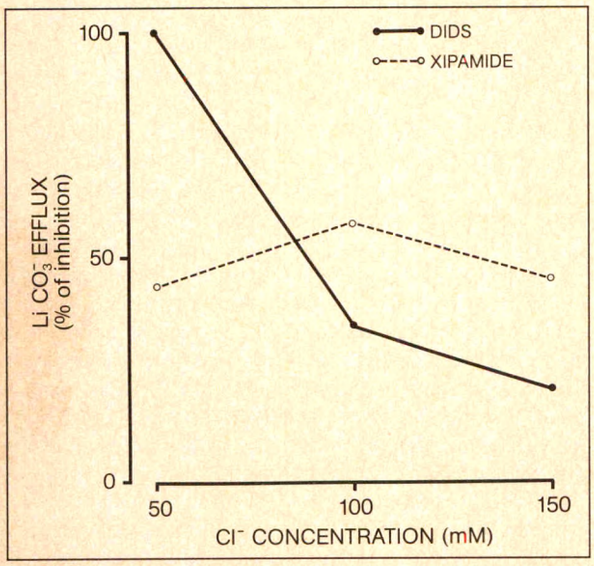


FIGURE 2. The effect of different concentrations of chloride (Cl^-) on the inhibition of the erythrocyte HCO_3^-/CL^- anion exchanger by DIDS and xipamide. When cells were incubated in the presence of a constant inhibitory dose of DIDS, increasing external chloride progressively decreased the level of inhibition of the anion exchanger. In contrast, no interaction was observed between xipamide and chloride. Similar results were observed in 5 other experiments. (The activity of the anion exchanger was evaluated by measuring the DIDS-sensitive $LiCO_3^-$ efflux from erythrocytes previously loaded with Li_2CO_3.)

Diuretics acting at nontranslocating sites: Canrenone is the active metabolite of spironolactone. Its mechanism of action was supposed to involve a competition with aldosterone for a common cytosolic receptor in distal and collecting tubules of the nephron.[9] However, canrenone also acts like a partial agonist at the digitalis receptor site of the erythrocyte Na^+, K^+ pump.[10] Therefore, the interaction of canrenone with the renal Na^+, K^+ pump in producing natriuresis may involve an additional mechanism.

Another example of a drug possibly acting at regulatory sites is xipamide, a loop diuretic that inhibits a bicarbonate (HCO_3^-)/Cl^- anion exchanger in human red cells.[11] Because xipamide does not interfere with the inhibition of anion exchanger by stilbene disulfonates such as 4,4′-diisothiocyano-2,2′-stilbene-disulfonic acid (DIDS) (Fig. 1), and the IC_{50} for xipamide is not modified by the presence of anions such as Cl^- (Fig. 2), this compound may inhibit the anion exchanger by binding to an inhibitory site(s) at the extracellular surface of the membrane (Fig. 3).[12]

From these studies it is suggested that xipamide might affect Na^+ reabsorption by inhibiting the HCO_3^-/Cl^- anion exchanger located at the thick ascending limb of Henle's loop.[13]

NEW TRENDS AND FURTHER DEVELOPMENTS

It is accepted that the genetic and hormonal factors determining the activity of ion transporters in cardiovascular and renal cells provide mechanisms to regulate blood pressure and renal Na^+ excretion (see reference 14 for review). For instance, the activation of vascular Na^+/H^+ exchange by vasoactive agents such as angiotensin II reduces Na^+ gradient for calcium ion (Ca^{2+}) extrusion by Na^+/Ca^{2+} exchange and produces vasoconstriction (see reference 15 for review).

In this regard, the study of the effects of diuretics on ion transport systems in human red blood cells can pro-

vide an assessment of the procedure to design new molecules with increased therapeutic efficacy in clinical conditions such as hypertension.

Thus, although amiloride is a weak inhibitor of the Na^+/H^+ exchanger, the presence of carbon chains on the 5 amino position of the pyrazine ring of amiloride increases the inhibitory potency of the molecule; the best compound so far is N-5-ethylisopropylamiloride, which can be as much as 200 times more potent than amiloride.[16,17]

Direct inhibition of Na^+/Ca^{2+} exchange may also represent a potential mechanism to produce vasodilation. Indapamide, a nonthiazide diuretic, seems to act primarily on the plasma membrane of spontaneously active smooth muscles by reducing the inward calcium ion current.[18] If this effect is responsible for the antihypertensive properties of the compound, further investigation is required.

CONCLUSION

Studies of the effects of diuretics on ion transport mechanisms have contributed to the knowledge of their molecular mechanisms of action. This is actually translated into the development of structure-activity investigations addressed to enhance the clinical applications of these drugs by increasing the number of their potential target cells and mechanisms.

REFERENCES

1. Kokko JP. Site and mechanism of action of diuretics. *Am J Med 1984; 76:suppl:11–17.*

2. Garay RP. Use of human red blood cells for the search of potent and specific inhibitors of ion transport mechanisms: therapeutical implications. In: Jorgensen PL, Verna R, eds. Advances in Biotechnology of Membrane Ion Transport. *New York: Raven Press, 1988;225–233.*

3. Haas M, McManus TJ. Bumetanide inhibits (Na+K+Cl) co-transport at a chloride site. *Am J Physiol 1983;245:C235–C240.*

4. Chipperfield AR. The (Na^+-K^+-Cl^-) co-transport system. *Clin Sci 1986;71: 465–476.*

5. Ellory JC, Stewart GW. The human erythrocyte C1-dependent Na-K cotransport system as a possible model for studying the action of loop diuretics. *Br J Pharmacol 1982;75:183–188.*

6. Frelin C, Vigne P, Barbry P, Lazdunski M. Molecular properties of amiloride action and of its Na^+ transporting targets. *Kidney Int 1987;32:785–793.*

7. Escobales N, Canessa M. Amiloride-sensitive Na^+ transport in human red cells: Evidence for a Na/H exchange system. *J Membr Biol 1986;90:21–28.*

8. Kinsella JL, Aronson PS. Amiloride inhibition of the Na^+-H^+ exchange in renal microvillus membrane vesicles. *Am J Physiol 1981;241:F374–F379.*

9. Marver D, Kokko JP. Renal target sites and the mechanism of action of aldosterone. *Miner Electrolyte Metab 1983;9:1–18.*

10. Garay RP, Diez J, Nazaret C, Dagher G, Abitbol JP. The interaction of canrenone with the Na^+, K^+ pump in human red blood cells. *Arch Pharmacol 1985;329:311–315.*

11. Nazaret C, Diez J, Hannaert PA, Christen MO, Wierzbicki N, Garay RP. Inhibition of the $Cl^-/NaCO_3^-$ anion exchanger by xipamide in human red blood cells. *Eur J Pharmacol 1987;144:353–362.*

12. Diez J, Arrazola A, Esparaza N, Miqueo C. The effects of loop diuretics on the HCO_3^-/Cl^- anion exchanger in human red blood cells. In: Jorgensen PL, Verna R, eds. Advances in Biotechnology of Membrane Ion Transport. *New York: Raven Press, 1988;235–245.*

13. Friedman PA, Andreoli TE. CO_2-stimulated NaCl absorption in the mouse renal cortical thick ascending limb of Henle. Evidence for synchronous Na^+/H^+ and Cl^-/HCO_3^- exchange in apical plasma membranes. *J Gen Physiol 1982;80:683–711.*

14. Canessa M, Brugnara C, Escobales N. The Li^+-Na^+ exchange and Na^+ -K^+-Cl^- cotransport systems in essential hypertension. *Hypertension 1987;10:suppl I:4–10.*

15. Aviv A. The link between cystolic Ca^{2+} and the Na^+-H^+ antiport: an unifying factor for essential hypertension. *J Hypertens 1988;6:685–692.*

16. Vigne P, Frelin C, Cragoe EJ, Lazdunski M. Ethylisopropylamiloride: A new and highly potent derivative of amiloride for inhibiting the Na^+/H^+ exchange system in various cell types. *Biochim Biophys Res Comm 1983;116:86–90.*

17. Vigne P, Frelin C, Cragoe EJ, Lazdunski M. Structure activity relationships of amiloride and certain of its analogues in relation to the blockade of the Na^+/H^+ exchange system. *Mol Pharmacol 1984;25:131–136.*

18. Mironneau J. Indapamide-induced inhibition of calcium movements in smooth muscles. *Am J Med 1988;84:suppl 1B:10–14.*

Twenty-Four-Hour Blood Pressure Monitoring and Effects of Indapamide

Joan Ocon, MD, and Jose Mora, MD

Twenty-four-hour blood pressure (BP) monitoring with a noninvasive device (Kontron) has been used to assess the effect of a single dose of indapamide in a group of patients with essential hypertension.

Originally 23 patients were selected. Three patients withdrew from the study because of refusal to go through the second 24-hour recording. Eight of the remaining patients had to be excluded for technical reasons, which left 12 patients available for analysis. All patients received a single dose of indapamide, 2.5 mg/day. Before treatment began, a 24-hour BP control was performed, and a second one a month later (37 ± 8 days). The age of the patients was 46 ± 10 years. Diurnal BP (8 AM to 10 PM) and heart rate were, respectively, 148 ± 15/101 ± 6 mm Hg and 79 ± 9 beats/min; night BP (10 PM to 8 AM) was 131 ± 15/88 ± 7 mm Hg and heart rate 71 ± 10 beats/min. After therapy, diurnal BP was 131 ± 15/92 ± 7 mm Hg (−15 ± 7/−8 ± 4: $p < 0.0001$/$p < 0.0001$); heart rate 82 ± 8 beats/min (difference not significant); night BP was 115 ± 13/80 ± 8 mm Hg (−16 ± 11/−8 ± 7: $p < 0.0001$/$p < 0.0001$) and heart rate 70 ± 9 beats/min (difference not significant). Twenty-four-hour systolic work values were 106 ± 15 at the beginning of the trial and 96 ± 14 (−9.7 ± 14; $p < 0.05$) after 1 month of indapamide treatment. Variability did not change with treatment.

These results confirm that 24-hour BP monitoring gives better information on response to treatment and that indapamide decreases BP in mild and moderate hypertension throughout the day while systolic work decreases only during nighttime.

(Am J Cardiol 1990;65:58H–61H)

Numerous studies have proved that continuous recordings of blood pressure (BP) over periods of 24 hours or more are very useful in the assessment of individual variations of BP throughout the day as well as in evaluating responses to drug treatment. Other studies concerning relationships of left ventricular mass and complications of hypertension with ambulatory BP have shown better correlations than with casual BP readings.[1–4] The last, but not least, advantage of this technique has been the avoidance of so-called white coat hypertension, since it decreases the conditions for the alert reaction to appear.[5,6]

Two methods are currently available, the intraarterial, which requires an invasive technique, and the noninvasive, based on the oscillation or auscultation of the pressure waves and signals. Both techniques have advantages and shortcomings. The invasive method, in which the recording is made for ultimate beat-to-beat analysis, is the more exact and can be used in basic cardiovascular research; however, it is difficult to use it in the same patient more than once because of its aggressive approach and the risk of any catheterization. Noninvasive methods do not have these disadvantages; they can be used as many times as deemed necessary, patient adaptability being the main factor to consider. On the other hand, they bring only a discontinuous line of information on function in the programmed periods, and their correspondence with the beat-to-beat analysis is not considered adequate. Nevertheless, their use in studying the effects of drugs in clinical trials with large numbers of patients is quite satisfactory.[7–10]

In this study, our purpose was to document the effects of indapamide, an antihypertensive diuretic drug, on 24-hour BP with the use of a noninvasive method.

METHODS

The study was designed as an open trial. Among the last 50 patients who underwent 24-hour BP monitoring, a group of 23 with mild to moderate essential hypertension (class 1 as defined by the World Health Organization) who required treatment were chosen. The mean daytime diastolic BP (8 AM to 10 PM) computed from the basal recording was used for inclusion criteria. These patients were required to have no antihypertensive medication for at least 2 weeks before the beginning of the study. Once the first 24-hour BP recording and selection of patients were performed, indapamide was prescribed at a daily dosage of 2.5 mg in the morning, and a second recording was performed 4 or 5 weeks later.

ICR 5300 Ambulatory Blood Pressure System from Spacelabs was used in this study. The recorder was set every 60 minutes during both awake (8 AM to 10 PM) and

From the Hypertension Unit, Nephrology Service, Fundacion Puigvert, Barcelona, Spain.

Address for reprints: Joan Ocon, MD, Hypertension Unit, Nephrology Service, Fundacion Puigvert, Barcelona, Spain.

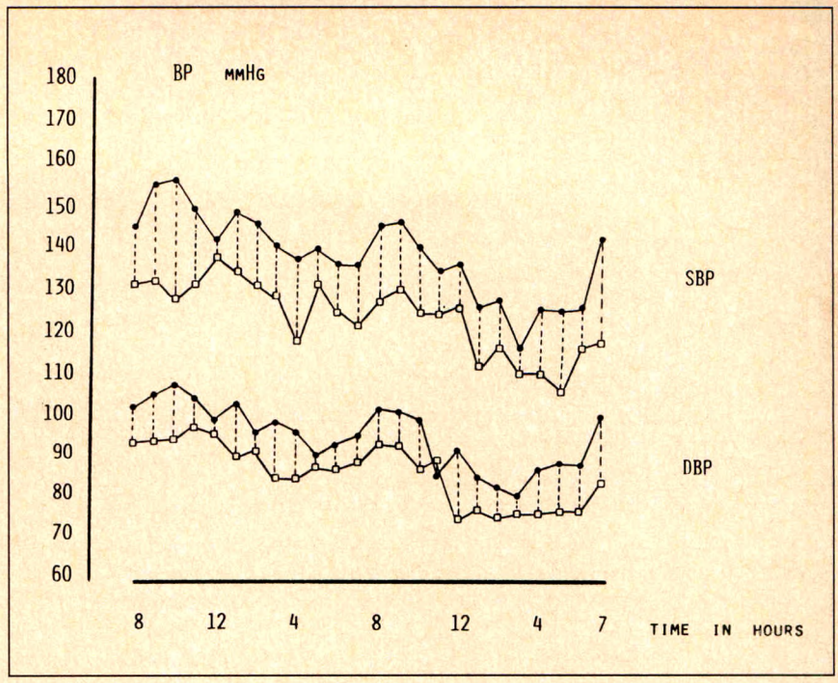


FIGURE 1. Blood pressure (BP) recording over 24 hours. *Circles*, before treatment; *squares*, after indapamide treatment. DBP = diastolic blood pressure; SBP = systolic blood pressure.

sleep (10 PM to 8 AM) periods. The results of systolic and diastolic BP measurements were expressed as the mean of each period ± standard deviation.

Heart rate and BP variability were evaluated from the standard deviation of the mean for each period of time studied in a single patient; when considering the results for the whole group the mean values were derived from the means of all individual values. Systolic work index was the product of mean daytime or nighttime systolic BP and the corresponding mean heart rate.

Potential differences between waking and sleeping BP as well as in the early increase in BP frequently observed after 6 AM before and after indapamide treatment were analyzed.

In all patients, a brief questionnaire of possible side effects was conducted at the end of the trial, and basic blood chemistry data (serum creatinine, sodium and potassium) were obtained in each patient.

Statistical analysis was performed by paired and unpaired comparisons of means applying Student *t* test.

RESULTS

From the 23 original patients included in the study, 3 refused to undergo the second recording of BP and their data were not used for the final report. Twenty patients completed the trial with two 24-hour BP monitorings; however, 8 had to be discarded for various reasons: 3 for disconnection of the monitor during the night and 5 for unreliable readings. Data from 12 patients were therefore kept for the analysis and only these data are shown here. The patients (5 men, 7 women), aged 46 ± 10 years, had mild to moderate essential hypertension, with normal results on physical examination and normal renal function as required by the protocol.

During the day period, mean initial systolic/diastolic BP was 148 ± 15/101 ± 6 mm Hg and mean heart rate

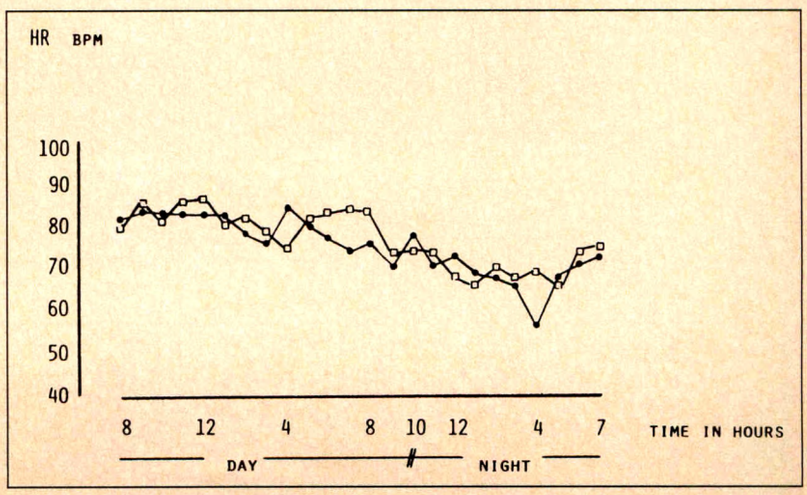


FIGURE 2. Heart rate (HR) recording over 24 hours. *Circles*, before treatment; *squares*, after indapamide treatment.

TABLE I Mean Systolic and Diastolic Blood Pressures During Day and Night Periods Before and After Treatment with Indapamide

		Day	Night	24-Hour
No treatment	SBP	148 ± 15	131 ± 15	140 ± 14
	DBP	101 ± 6	88 ± 7	96 ± 6
Indapamide	SBP	131 ± 15 = −15* (−11%)	115 ± 13 = −16* (−12%)	125 ± 13 = −15* (−11%)
	DBP	92 ± 7 = −8* (−9%)	80 ± 8 = −8* (−9%)	87 ± 6 = −8* (−9%)

* p <0.001.
Values are mean ± standard error of the mean.
DBP = diastolic blood pressure; SBP = systolic blood pressure.

TABLE II Cardiac Work Index During Day and Night Periods Before and After Treatment with Indapamide

	Day	Night	24-Hour
No treatment	115 ± 17	92 ± 18	106 ± 15
	NS	p <0.05	p <0.05
Indapamide	106 ± 17	88 ± 14	96 ± 14

p <0.05, paired comparisons.
Values are mean ± standard error of the mean.
NS = not significant.

79 ± 9 beats/min; during the night period, mean initial systolic/diastolic BP was 131 ± 15/88 ± 7 mm Hg and mean heart rate 71 ± 10 beats/min. Twenty-four-hour BP and heart rate profiles before and after indapamide treatment are shown in Figures 1 and 2. After 1 month of treatment, we observed an average decrease of mean systolic/diastolic BP of 15 ± 7/8 ± 4 mm Hg during the day period and 16 ± 11/8 ± 7 mm Hg during the night period, both reaching high statistical significance (p <0.0001, Table I). Heart rate did not show any statistically significant change at any time.

The results of cardiac work index for both periods, before and after indapamide treatment, are listed in Table II. If we consider the day period, systolic work index decreased from 115 ± 17 to 106 ± 17 mm Hg after 1 month of therapy, but this was not statistically significant. Conversely, the decrease observed for the night period (from 92 ± 18 to 80 ± 14) was statistically significant (p <0.05). Systolic work index for the whole day period also demonstrated a significant change (from 106 ± 15 to 96 ± 14, p <0.05).

Variability of BP derived from the standard deviation of the mean as stated did not show any significant change when the 24-hour period was considered; when the day and night periods were considered separately, only systolic BP variability at night was significantly reduced (p <0.05, Table III).

An analysis of the 24-hour BP recording was performed to find the most accurate time for BP evaluation when measured by conventional casual methods. Subperiods of time were studied and their diastolic differences compared. Table IV indicates that the best time to check BP in the untreated group is between 8 and 10 AM, and in the treated group any time after 8 AM.

No significant changes were perceived in the increase in BP observed in the early morning hours before and after treatment.

Biochemical parameters showed no changes of any clinical relevance: serum creatinine varied from 97.24 ± 17.68 to 106.08 ± 26.52 μmol/liter, serum sodium from 141 ± 2 to 142 ± 3 mmol/liter, serum potassium from 4.3 ± 0.2 to 4.2 ± 0.2 mmol/liter, and serum uric acid from 333.1 ± 71.4 to 356.9 ± 5.9 mmol/liter. Tolerance was good and no patient complained of adverse effects that could be attributed to the drug.

TABLE III Blood Pressure Variability Before and After Treatment with Indapamide

		Day	Night	24-Hour
No treatment	SBP	13 ± 6	16 ± 8	17 ± 7
	DBP	9 ± 4	9 ± 3	11 ± 4
Indapamide	SBP	13 ± 5	9 ± 3*	15 ± 6
	DBP	8 ± 2	7 ± 2	11 ± 3

Values are mean ± standard error of the mean, paired comparisons.
* p <0.05.

DISCUSSION

Indapamide, a sulfonamide derivative, owes its antihypertensive properties more to its vascular than to its renal effects.[11] Used as a single dose of 2.5 mg/day, it has been shown to be both effective and safe in patients with mild to moderate essential hypertension.[12] It does not exert any deleterious effect on renal function; in our study, serum creatinine has remained unchanged. Furthermore, it does not affect either cardiac performance or contractility.[12] As previously described, the sympathetic nervous system is not activated, and in this study, indapamide did not produce any reactive or reflex tachycardia and did not modify the decrease in heart rate observed

TABLE IV Comparison of Different Subperiods of Time for Diastolic Blood Pressure Before and After Treatment with Indapamide

	5 Hours		6 to 8 Hours		8 to 10 Hours	11 to 22 Hours	8 to 22 Hours
No treatment	88 ± 8	= +8 ± 3 p <0.05	96 ± 10	= +8 ± 1.7 p <0.0001	104 ± 9	99 ± 6	101 ± 6
Indapamide	76 ± 9	= +8 ± 2.3 p <0.001	84 ± 12		93 ± 7	92 ± 7	92 ± 7

during the sleeping hours.[13] When the 24-hour BP mean is considered, a decrease in cardiac work index was observed and was related to the decrease in cardiac afterload. Even if this is a very indirect physiologic measurement, it nevertheless helps to perceive the improvement in afterload which is not overrun by an undesirable increase in heart rate.

Indapamide's ability to reduce hypertension has already been widely recognized, and comparative trials with some of the new antihypertensive drugs point to similar efficacy and tolerance,[14,15] giving a good combination of both qualities.[16] None of the patients who had to be excluded from our study complained of adverse effects; it was the technique used that for different reasons forced the decision to withdraw. In addition, indapamide has been shown to improve the patient's quality of life.[15–18]

BP decreased by about 11% for the systolic measurement and 9% for diastolic measurement. The decrease was the same for both day and night periods. We have previously observed in patients with essential hypertension a difference between day and night readings of about 13% for systolic and diastolic BP and heart rate, irrespective of the basal BP values. In this study, the difference between day and night readings was maintained with indapamide treatment. Without indapamide, the day-night difference is 11% for systolic BP, 13% for diastolic BP and 10% for heart rate. These differences remain the same after 1 month of treatment with indapamide, being 12% for systolic BP, 13% for diastolic BP and 14% for heart rate. Indapamide does not interfere with the central mechanisms for BP reduction during the night,[19] thus maintaining the classic curve of circadian rhythm for the BP.

Twenty-four-hour BP recording has many advantages over casual readings. These include the avoidance of the patient's alert reaction and the possibility of obtaining a continuous view of the BP behavior throughout a time period long enough to observe nycthemeral changes as well as the response to treatment.[20] Nevertheless, 24-hour BP monitoring presents a number of limitations. Some of the devices are heavy, troublesome and noisy. Moreover, when the periods between BP recordings are too short, the procedure may interfere with the patient's daily activities. Correlation of the values obtained by 24-hour BP recording with the intraarterial recordings is not always satisfactory; however, these discrepancies become insignificant when a large number of patients are investigated.[21]

CONCLUSION

Twenty-four-hour continuous monitoring of BP is very useful in the assessment of the response to antihypertensive drugs. Control of BP proved to be easily and effectively documented using 24-hour recording; however, patient cooperation is essential in obtaining satisfactory recordings. Indapamide has been shown to be most effective throughout the 24-hour period; it does not disturb circadian rhythm, and it decreased cardiac work index without affecting heart rate. BP variability does not change. No adverse effects were reported by any of the patients, and blood parameters were not affected.

REFERENCES

1. Weber MA. Whole day blood pressure. *Hypertension 1988;11:288–299.*

2. Rowlands DB, Ireland MA, Glover DR, McLeay RA, Stallard TJ, Littler WA. The relationships between ambulatory blood pressure and echocardiographically assessed left ventricular hypertrophy. *Clin Sci 1981;61:suppl 7:101s–103s.*

3. Drayer JIM, Weber MA, DeYoung JL. Blood pressure as determinant of cardiac left ventricular mass. *Arch Intern Med 1983;143:90–92.*

4. Perloff D, Solokow M, Cowan R. The prognostic value of ambulatory blood pressure. *JAMA 1983;249:2793–2798.*

5. Mancia G, Parati G, Pomidossi G, Grassi G, Casadei R, Zanchetti A. Alerting reaction and rise in blood pressure during measurement by physician and nurse. *Hypertension 1987;9(2):209–215.*

6. Mancia G, Bertinieri G, Grassi G, Parati G, Pomidossi G, Ferrari A, Gregorini L, Zanchetti A. Effect of blood pressure measurement by the doctor on patient's blood pressure and heart rate. *Lancet 1983;2:695–697.*

7. Cassadei R, Parati G, Pomodossi G, Groppelli A, Trazzi S, DiRienza M, Mancia G. 24-hour blood pressure monitoring: evaluation of Spacelabs 5300 monitor by comparison with intra-arterial blood pressure recording in ambulant subjects. *J Hypertens 1988;6:797–804.*

8. Weber MA, Drayer JIM. Role of blood pressure monitoring in the diagnosis of hypertension. *J Hypertens 1986;4:suppl 5:S325–S327.*

9. Conway YJ, Johnston J, Coats A, Somers V, Sleight P. The use of ambulatory blood pressure monitoring to improve the accuracy and reduce the number of subjects in clinical trials of antihypertensive agents. *J Hypertens 1988;6(2):111–116.*

10. Pickering TG, Harshfield GA, Devereux RB, Laragh JH. What is the role of ambulatory blood pressure monitoring in the management of hypertensive patients? *Hypertension 1985;7(2):171–177.*

11. Drug Therapy in Hypertension. In: Drayer JIM, Lowenthal DT, Weber MA, eds. Clinical Pharmacology. *New York: Marcel Dekker, 1987:82–83.*

12. Leenen FH, Smith DL, Farkas RM, Boer WH, Reeves RA, Marquez-Julio A. Cardiovascular effects of indapamide in hypertensive patients with or without renal failure. A dose response curve. *Am J Med 1988;84:suppl 1B:76–85.*

13. Floras JS, Hassan MO, Jones JV, Osikowska BA, Sever PS, Sleight P. Factors influencing blood pressure and heart rate variability in hypertensive humans. *Hypertension 1988;11(3):273–281.*

14. Chaignon M, Luckso M, Rapoud JP, Aubert P, Guedon J. Comparative effects of nifedipine and indapamide in the treatment of arterial hypertension. *Arch Mal Coeur 1985;78:67–72.*

15. Lacourcière Y. Analysis of well-being and 24-hour blood pressure recording in a comparative study between indapamide and captopril. *Am J Med 1988;84: suppl 1B:47–52.*

16. Werning C, Weitz T, Ludwig B. Assessment of indapamide in elderly hypertensive patients with special emphasis on well-being. *Am J Med 1988;84:suppl 1B:104–108.*

17. Well-being, hypertension and indapamide. Proceedings of the XVth International Meeting. November 8, 1986, Rome, Italy. *Am J Med 1988;84:suppl 1B:1–109.*

18. Watters K, Campbell B. Can an antihypertensive agent be both effective and improve the quality of life? A multicentre study with indapamide. *Br J Clin Pract 1986;40(6):239–244.*

19. Van Egeren LF. Repeated measurements of ambulatory blood pressure. *J Hypertens 1988;6:753–756.*

20. Raftery EB. Understanding hypertension: the contribution of direct ambulatory blood pressure monitoring. In: Weber MA, Drayer JIM, eds. Ambulatory Blood Pressure Monitoring. *New York: Springer-Verlag, 1984;105–116.*

21. Di Rienzo M, Grassi G, Pedotti A, Mancia G. Continuous vs intermittent blood pressure measurements in estimating 24-hour average blood pressure. *Hypertension 1983;5(2):264–269.*

Clinical Efficacy and Quality of Life with Indapamide Alone or in Combination with Beta Blockers or Angiotensin-Converting Enzyme Inhibitors

Dimitrios I. Athanassiadis, MD, Constantinos G. Dimopoulos, MD, Alexandros K. Tsakiris, MD, Dionyssios F. Cokkinos, MD, Achileas A. Tourkantonis, MD, Pavlos K. Toutouzas, MD, Bernard Boutin, MD, and David Guez, MD

A multicenter study was performed to assess the efficacy and the acceptability of indapamide in hypertensive patients previously untreated, or treated and unsatisfactorily controlled with either angiotensin-converting enzyme (ACE) inhibitor or β-blocking therapy.

Four centers participated in the study, which included patients whose supine diastolic blood pressure was between 95 and 115 mm Hg with no treatment (group I, n = 40), those taking captopril (group II, n = 40) or those taking propranolol (group III, n = 40). After a 2-week single-blind placebo run-in period, patients received indapamide either alone (group I) or in combination with the previous therapy (groups II and III) for 4 months. Blood pressure, heart rate, weight, and clinical and biochemical acceptability were measured before and after 2 and 4 months of treatment. At the same time points, quality of life was determined using standardized questionnaires completed by the patient (20 items) and the physician (10 items) and a visual analog scale completed by the patient.

In all groups, administration of indapamide induced a clinically and statistically significant reduction in both systolic and diastolic blood pressures in the supine position after 2 months. Indapamide alone controlled blood pressure in 82% of the patients previously untreated, and indapamide in combined therapy controlled blood pressure, respectively, in 67 and 85% of patients previously uncontrolled with ACE inhibitors or β blockers.

In all groups, questionnaires on quality of life showed a progressive and significant improvement in general well-being. After 4 months of treatment, the percentage of improvement in the physician questionnaire was 77.1% in group I, 60.6% in group II and 71.4% in group III. Similar results were obtained with the patient questionnaire.

Biochemical acceptability was characterized by the stability of all parameters, including sodium, potassium, glucose, creatinine, cholesterol and triglycerides and a slight increase in uric acid in all groups.

These results confirm the satisfactory efficacy and acceptability of indapamide and its beneficial effects on quality of life when administered as a first-step therapy as well as in combination with β blockers or ACE inhibitors.

(Am J Cardiol 1990;65:62H–66H)

High blood pressure is currently one of the major health problems. Numerous trials have demonstrated the benefits of long-term treatment of mild to moderate essential hypertension in terms of a reduction in cardiovascular morbidity and mortality.[1]

Diuretics have long been considered a major antihypertensive treatment. Most of the large clinical trials were conducted with these agents as "first step" therapy.[1] However, many antihypertensive drugs have become available over the last 10 years and, according to the latest report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure, β blockers, angiotensin-converting enzyme (ACE) inhibitors and calcium antagonists as well as diuretics can now be used as initial therapy.[2] Nonetheless, diuretics remain, in many countries, the "corner stone" in the treatment of hypertension principally because of the low incidence of side effects associated with their use and the reasonable cost of therapy.[3]

Indapamide has been available for more than 10 years and its efficacy and acceptability as an antihypertensive drug have been established in numerous studies.[4] Moreover, although it is classified as a diuretic, indapamide has several distinct pharmacologic properties: at the therapeutic dose commonly used (2.5 mg once daily), indapamide has a limited diuretic effect, which suggests that its antihypertensive activity might be related more to its vascular properties than to its renal effects[4]; and indapa-

From the Department of Cardiology and Hypertension, Red Cross Hospital, Athens, Greece; Department of Cardiology and Hypertension, Tzanion Hospital, Pireus, Greece; First Department of Internal Medicine, University of Salonica, Achepa Hospital, Salonica, Greece; Department of Cardiology, University of Athens, Hippokration Hospital, Athens, Greece; and Institut de Recherches Internationales Servier, Neuilly-sur-Seine, France.

Address for reprints: Dimitrios I. Athanassiadis, MD, Department of Cardiology and Hypertension, Red Cross Hospital, Athens, Greece.

mide is not associated with one of the major side effects of diuretics, namely, alterations in lipid metabolism.[4–7]

We report the results of a multicenter study conducted in Greece with patients receiving indapamide either alone or in combination with β blockers or ACE inhibitors for a period of 4 months.

METHODS

Patients: Male or female patients eligible for the study were aged between 18 and 65 years and had mild to moderate essential hypertension, which was either not treated previously or not controlled with a drug regimen consisting of either an ACE inhibitor (captopril) or a β blocker (propranolol).

These patients were given placebo, alone or in combination with their previous treatment (ACE inhibitor or β blocker) for 2 weeks. At the end of this period, indapamide, 2.5 mg/day, was given to patients who fulfilled the inclusion criterion of stable hypertension (defined by a mean supine diastolic blood pressure between 95 and 115 mm Hg), appeared to be compliant, and did not meet the following exclusion criteria: secondary hypertension, severe hypertension defined by a supine diastolic blood pressure >115 mm Hg, complicated hypertension (i.e., symptomatic coronary artery disease, heart failure, renal insufficiency, stage III or IV optic fundus), presence of a metabolic or hepatic disorder or any other severe chronic disease, concomitant medication including corticosteroids, nonsteroidal anti-inflammatory drugs, neuroleptics, antidepressants or lithium, and weight >30% of the midpoint of recommended weight. Therapy with ACE inhibitors or β blockers, when given previously, was continued at the same dosage. After 2 months of treatment, patients with satisfactory blood pressure control (mean supine diastolic blood pressure <90 mm Hg) and without serious side effects continued the same drug regimen for a further 2 months.

Four centers participated in the study, and each enrolled 30 patients. Ten patients received indapamide alone (group I), 10 received indapamide and ACE inhibitors (group II) and 10 received indapamide and β blockers (group III).

Patient evaluation: Patients were examined by the same investigator in each center throughout the course of the study. Visits were scheduled on the day of enrollment, at the end of the placebo period, and then 2 and 4 months after the start of indapamide treatment.

At each visit, a full physical examination was performed, body weight, blood pressure and heart rate were measured, and the presence of adverse effects, acceptability and quality of life were evaluated.

Blood pressure was measured by means of a mercury sphygmomanometer. Supine blood pressure was measured after 10 minutes at rest and the mean of 3 measurements at 1-minute intervals was calculated. Erect blood pressure was measured after 2 minutes of standing. Diastolic blood pressure was defined as the point of disappearance of the Korotkoff sounds (phase V). Heart rate was measured by cardiac auscultation over a period of 1 minute under the same conditions.

TABLE I Characteristics of Patients

	Indapamide	Indapamide + ACE Inhibitors	Indapamide + Beta Blockers
No. of pts.	40	40	40
Sex ratio (M/F)	1.1	0.73	0.53
Age (years) (range)	51.3 ± 1.4 (31–65)	50.8 ± 1.2 (32–64)	53.4 ± 1.3 (38–65)
Supine DBP (mm Hg)	100.3 ± 0.6 (95–115)	100.9 ± 0.6 (95–115)	100.7 ± 0.7 (95–112)

Values are expressed as mean ± standard error of the mean.
ACE = angiotensin-converting enzyme; DBP = diastolic blood pressure.

Treatment acceptability was assessed from complaints either reported spontaneously or elicited after direct questioning.

Quality of life was evaluated using 3 different tests[8]: a questionnaire filled in by the physician, a questionnaire completed by the patient and a visual analog scale. The physician's questionnaire consisted of multiple items under the following 10 headings: appearance, language, muscular and sensory fatigue, visceral functional disorders, sleep, intellectual fatigue, emotion and mood, anxiety, concentration and character. The patient's questionnaire consisted of 20 assertions based on the same headings. A score ranging from 0 (absence of symptoms) to 5 (according to the severity of the symptoms) was applied to each item. The visual analog scale provided another tool for evaluation of quality of life. At each visit, patients were asked to place a cross on the scale ranging from "good" to "bad" corresponding to the way they felt.

Other investigations were performed at the time of entry and after 2 and 4 months of indapamide treatment: 12-lead electrocardiography and routine laboratory tests, including blood cell counts, plasma electrolytes, proteins, creatinine, calcium, phosphate, urate, glycemia, total cholesterol and triglycerides.

Statistical analysis: Results from each group were analyzed separately and expressed as mean ± standard error of the mean.

A 2-way analysis of variance (time-patients) was used to evaluate changes in blood pressure and heart rate, evolution of quality of life, and modifications of biochemical parameters throughout the placebo and the treatment periods. When statistical significance was attained ($p < 0.05$), analysis was completed by a Newman-Keuls test for multiple comparisons of time points.

Evolution of mean score obtained for each item of the quality of life questionnaire was evaluated by a Friedman test and, in the case of a significant time effect, by a Newman-Keuls test.

RESULTS

One hundred twenty patients entered the study. At each center 10 patients were entered into each of the 3 groups.

Mean age of the patients were respectively, 51.3 ± 1.4 years (range 31 to 65) in group I, 50.8 ± 1.2 years (range 32 to 64) in group II and 53.4 ± 1.3 years (range 38 to 65)

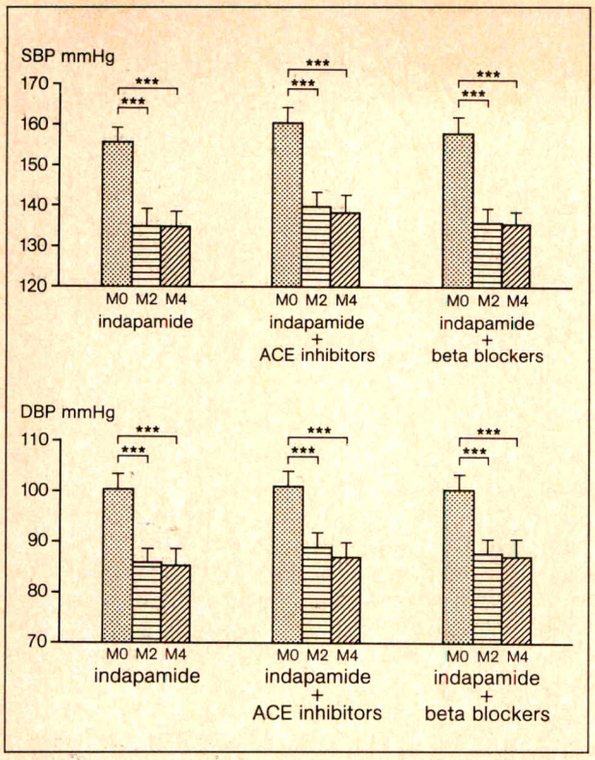


FIGURE 1. Effects of indapamide on supine and standing systolic (SBP) and diastolic (DBP) blood pressure after 2 and 4 months of indapamide treatment. ACE = angiotensin-converting enzyme inhibitors; ***p <0.001.

TABLE II Supine and Standing Systolic (SBP) and Diastolic (DBP) Blood Pressure and Heart Rate (HR) at Baseline and After 4 Months of Indapamide Treatment

	Indapamide	Indapamide + ACE Inhibitors	Indapamide + Beta Blockers
Supine SBP (mm Hg)	155.5 ± 2.7	160.6 ± 2.6	157.8 ± 2.5
	134.9 ± 2.1†	138.3 ± 2.6†	134.9 ± 2.0†
Supine DBP (mm Hg)	100.3 ± 0.7	100.9 ± 0.7	100.2 ± 0.6
	85.5 ± 0.9†	87.2 ± 1.2†	87.3 ± 1.1†
Supine HR (beats/min)	75.9 ± 1.4	72.9 ± 1.1	69.1 ± 1.5
	74.6 ± 1.3	72.8 ± 1.3	66.6 ± 1.2
Standing SBP (mm Hg)	151.4 ± 2.4	157.8 ± 3.2	156.1 ± 2.4
	131.1 ± 2.0†	134.5 ± 2.7†	129.2 ± 1.7†
Standing DBP (mm Hg)	101.3 ± 0.8	103.7 ± 1.0	101.7 ± 0.7
	87.9 ± 1.1†	88.7 ± 1.3†	87.6 ± 1.1†
Standing HR (beats/min)	82.4 ± 1.5	77.9 ± 1.2	73.6 ± 1.6
	79.9 ± 1.4	78.1 ± 1.3	70.1 ± 1.1*

* p <0.05; † p <0.001.
Values are expressed as mean ± standard error of the mean.

TABLE III Assessment of Quality of Life by the Mean of Physician's and Patient's Questionnaires

	Indapamide	Indapamide + ACE Inhibitors	Indapamide + Beta Blockers
Physician's questionnaire	10.3 ± 1.3	12.0 ± 1.6	10.3 ± 1.4
(global score)	5.3 ± 0.8*	8.6 ± 1.2*	7.3 ± 1.0*
Patient's questionnaire	16.5 ± 1.9	22.5 ± 3.0	22.1 ± 3.1
(global score)	10.3 ± 1.7*	17.2 ± 2.8*	15.2 ± 2.4*

* p <0.001.
Values are expressed as mean ± standard error of the mean.
ACE = angiotensin-converting enzyme.

in group III. The male-female ratios were, respectively, 1.1 in group I, 0.73 in group II and 0.53 in group III. General characteristics of the study population are summarized in Table I.

Analysis of the data revealed a slight but statistically significant decrease in blood pressure throughout the run-in placebo period, except in patients receiving ACE inhibitor therapy. At the time of inclusion, mean supine diastolic blood pressure was, respectively, 100.3 ± 0.6 mm Hg (range 95 to 115) in group I, 100.9 ± 0.6 mm Hg (range 95 to 115) in group II and 100.7 ± 0.7 mm Hg (range 95 to 112) in group III. A highly statistically significant decrease in supine and standing heart rate (3.5 and 3.4 beats/min) was observed during the run-in period in patients receiving β blockers ($p < 0.01$).

With regard to quality of life, the condition of the patients remained quite stable during that period; nevertheless, the mean score from the visual analog scale indicates a certain degree of improvement in patients receiving ACE inhibitor therapy ($p < 0.05$).

Ninety-eight patients completed the study. Thirteen patients were withdrawn at the second month because of the lack of blood pressure control : 3 of them belonged to group I, 4 to group II and 6 to group III. The remaining 9 patients either withdrew because of noncompliance or were lost to follow-up.

In all groups, indapamide induced a highly statistically significant reduction in systolic and diastolic blood pressures, in the supine and standing positions ($p < 0.001$) (Fig. 1). This decrease was recorded after 2 months of treatment and persisted until the end of the trial. After 4 months, mean reduction in supine systolic blood pressure was 20.6 mm Hg (group I), 22.3 mm Hg (group II) and 22.9 mm Hg (group III); in diastolic pressure it was 14.8 mm Hg (group I), 13.7 mm Hg (group II) and 12.9 mm Hg (group III). Mean reduction in standing systolic blood pressure was 20.3 mm Hg (group I), 23.3 mm Hg (group II) and 26.9 mm Hg (group III); in diastolic pressure it was 13.4 mm Hg (group 1), 15.0 mm Hg (group II) and 14.1 mm Hg (group III). There was no significant change in either standing or supine heart rates, except in patients receiving β blockers who had a decrease in standing heart rate of 3.5 beats/min from the first to fourth month ($p < 0.05$) (Table II).

Blood pressure control (supine diastolic blood pressure <90 mm Hg, supine systolic blood pressure <160 mm Hg) was obtained at the second month in 71% of the patients in group I, 51% in group II and 64% in group III, and at the fourth month in 82% of the patients in group I, 67% in group II and 85% in group III.

A noticeable improvement in quality of life was observed in each of the different tests. The patient's questionnaire showed improvement at month 4 in 73% of the patients in group I, 72% in group II and 80% in group III.

These results were similar to those obtained with the physician's questionnaire (77, 72 and 61% of the patients showed an improvement). The results are confirmed by a highly statistically significant decrease in mean gravity score between the first and fourth month ($p < 0.001$) when the results of both questionnaires are considered (mean reduction 42.9% in group I, 26.1% in group II and 30.3% in group III) (Table III), and by a highly statistically significant increase in mean well-being score based on visual analog scale (mean increase: 95% in group I, 48.5% in group II and 50% in group III) (Fig. 2). Analysis of the patient's questionnaire revealed a decrease in the mean score for each item between the first and fourth month and statistically significant change in 5 of these parameters mainly in patients in group I: ringing in the ears ($p < 0.01$), tiredness on effort ($p < 0.05$), loss of appetite ($p < 0.05$), anxiety ($p < 0.01$) and lack of dynamism ($p < 0.01$). If we consider the physicians questionnaire, positive changes were obtained in all groups for 4 items concerning language, sleep disorders, intellectual performance and anxiety.

A moderate reduction in body weight was observed during the study in all groups: Mean reduction between the first and fourth month was 1.2 kg in group I ($p < 0.05$) and group II ($p < 0.05$), and 0.8 kg ($p < 0.05$) in group III.

Biochemical parameters were measured at baseline and after 2 and 4 months of treatment (Table IV). There was a statistically significant change in uric acid, with a tendency to increase throughout the treatment period. The increase was observed at day 60 in groups I and III and at day 120 only in group II. Mean increase at day 120 was 12.0% in group I ($p < 0.01$), 20.3% in group II ($p < 0.001$) and 7.4% in group III ($p < 0.01$). A slight decrease in mean plama potassium was observed in each group which reached statistical significance in group III but remained within the limits of the normal range in every case. No change in lipid profile was observed in any patient.

DISCUSSION

The antihypertensive response observed when indapamide was prescribed alone is in agreement with the results of other multicenter studies.[9–12] In these trials, blood pressure control was observed in 70 to 80% of the patients, the maximal antihypertensive effect was obtained by 8 weeks and maintained over the following months, and a 10 to 20% reduction in both systolic and diastolic blood pressures was usually recorded.

By contrast, fewer studies have been conducted to investigate the efficacy of indapamide as a second-step therapy in patients who are resistant to β blockers or ACE inhibitors but they all demonstrate supplementary antihypertensive activity whether indapamide was given in combination with atenolol,[13] pindolol,[14,15] metoprolol[16] or captopril.[17,18] Our data confirm this benefit over a longer period and in a larger sample of patients previously treated with either propranolol or captopril.

With regard to the acceptability of indapamide, no major adverse effects related to treatment were reported during the study. In addition, quality of life improved in most patients. This advantage, which is crucial in the management of patients with mild to moderate essential hypertension, has been demonstrated when indapamide is given as monotherapy[8,18,19] but is now also demonstrated when indapamide is given as second-step therapy.

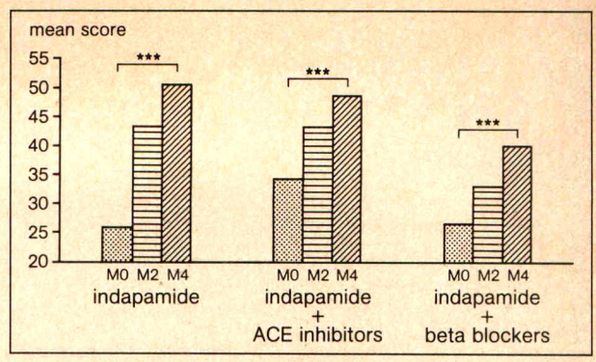


FIGURE 2. Assessment of quality of life by the mean of visual analog scale after 2 and 4 months of indapamide treatment. ***p <0.001; other abbreviations as in Figure 1.

One of the major properties of indapamide demonstrated in short- and long-term studies[4–7,20] relates to the lack of effect on lipid metabolism. In this study, no changes in lipid metabolism were reported in any group. Because changes in serum lipoproteins usually induced by diuretics have been implicated in the lack of prevention of coronary events in treated hypertensive patients, attention is focused on this property of indapamide. The only biochemical abnormality was a slight increase in plasma uric acid which was not constant and was asymptomatic because concentrations of serum acid uric did not exceed the upper limit of normal.[12] The lack of decrease in serum potassium, with the exception of group III, was probably a consequence of low dosage and dietary habits.[19]

In summary, this study confirms previous results which suggest that the efficacy, low incidence of adverse effects, and simple once-daily dosage of indapamide make it a very useful antihypertensive drug either as a first or a second choice of therapy in patients whose

TABLE IV Biochemical Parameters at Baseline and After Four Months of Indapamide Treatment

	Indapamide	Indapamide + ACE Inhibitors	Indapamide + Beta Blockers
Potassium	4.46 ± 0.07	4.33 ± 0.08	4.39 ± 0.07
(mEq/liter)	4.44 ± 0.07	4.19 ± 0.08	4.18 ± 0.07*
Uric acid (mg %)	5.33 ± 0.33	5.36 ± 0.25	5.29 ± 0.27
	5.98 ± 0.25†	6.45 ± 0.25‡	5.68 ± 0.30†
Creatinine (mg %)	1.04 ± 0.02	1.01 ± 0.03	1.01 ± 0.03
	1.03 ± 0.02	1.06 ± 0.04	1.28 ± 0.26
Cholesterol (mg %)	233.5 ± 8.00	237.6 ± 6.70	244.3 ± 7.10
	244.3 ± 8.00	242.6 ± 7.10	242.7 ± 8.50
Triglycerides (mg %)	132.9 ± 11.0	142.6 ± 8.50	141.9 ± 6.50
	124.6 ± 8.00	149.1 ± 8.00	152.6 ± 10.50

* $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$.
Values are expressed as mean ± standard error of the mean.
ACE = angiotensin-converting enzyme.

hypertension is not controlled with β blockers or ACE inhibitor therapy.

REFERENCES

1. Moser M. Treating hypertension: a review of clinical trials. *Am J Med 1986;81:suppl 6c:25–32.*

2. The 1988 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med 1988;148:1023–1038.*

3. Leonetti G, Terzoli L, Bragato R. Advantages and limitation of diuretic therapy in essential hypertension. *Am J Hypertens 1989;2:82S–85S.*

4. Cardona R, Lopez B, Fragachan F. Effects of indapamide on the lipid profile of patients with essential hypertension. In: Ogilvie RI, Safar M, eds. Indapamide and the Current Treatment of Hypertension. Proceedings of the XIV International Symposium on Indapamide. *London:John Libbey, 1986, 93–97.*

5. Meyer-Sabellek W, Gotzen R, Heitz J, Arntz HR, Schelte KL. Serum lipoprotein levels during long-term treatment of hypertension with indapamide. *Hypertension 1985;7:suppl II:170–174.*

6. Scalabrino A, Galeone F, Guintoli F. Clinical investigation on long-term effects of indapamide in patients with essential hypertension. *Curr Ther Res 1984;35:17–22.*

7. Weidmann P, Gerber A, Mordasini R. Effects of antihypertensive therapy on serum lipoproteins. *Hypertension 1983;5:suppl 3:120–131.*

8. Guez D, Crocq L, Safavian A, Labardens P. Effects of indapamide on the quality of life of hypertensive patients. *Am J Med 1988;84:suppl 1B:53–58.*

9. Abbou CB. The efficacy and tolerance of indapamide in essential hypertension: a multicenter study in 981 patients. *Curr Med Res Opin 1985;9:494–499.*

10. Beling S, Vukovich RA, Neiss ES, Zisblatt M, Webb E, Dosi M. Long term experience with indapamide. *Am Heart J 1983;106:258–262.*

11. Capone P, Vukovitch RA, Neiss ES, Bolton S, Reeves RL. Multicenter dose-response study of the effect of indapamide in the treatment of patients with mild to moderate hypertension. *Clin Ther 1983;5:305–316.*

12. Chaffman M, Heel RC, Brodgen RN, Speight TM, Avery GS. Indapamide: a review of its pharmacodynamic properties and therapeutic efficacy in hypertension. *Drugs 1984;28:189–235.*

13. De Divitiis O, Di Somma S, Pettito M, Fazio S, Ligouri V. Indapamide and atenolol in the treatment of hypertension: double blind comparative and combination study. *Curr Med Res Opin 1983;8:493–500.*

14. Chalmers JP, Wing LMH, Grygiel JJ, West MJ, Graham JR, Bune AJ. Effects of once daily indapamide and pindolol on blood pressure, plasma aldosterone concentration and plasma renin activity in a general practice setting. *Eur J Clin Pharmacol 1982;22:191–196.*

15. Rumboldt Z, Rumboldt M, Jurisic M. Indapamide versus beta-blocker therapy; a double blind, crossover study in essential hypertension. *Curr Med Res Opin 1984;9:10–20.*

16. Kubik MM, Coote JH. Comparison of the antihypertensive effects of indapamide and metoprolol. *Postgrad Med J 1981;57:suppl II:44–50.*

17. Galderisi M, Iacono C, Santomauro M, Ferraro S, Bonagura EC. Captopril and indapamide: comparison and combination in the treatment of hypertension. Abstract, 11th Scientific Meeting of the International Society of Hypertension. *Heidelberg, W Germany, Aug 31–Sept 6, 1986:472.*

18. Lacourcière Y. Analysis of well-being and 24 hour blood pressure recording in a comparative study between indapamide and captopril. *Am J Med 1988;84:suppl 1B:47–52.*

19. Leonetti G, Rapelli A, Salavetti A, Scanellato L. Tolerability and well-being with indapamide in the treatment of mild-moderate hypertension. *Am J Med 1988;84:suppl I B:59–64.*

20. Gerber A, Weidman P, Bianchetti MG. Serum lipoproteins during treatment with the antihypertensive agent indapamide. *Hypertension 1985;7:suppl II:164–169.*

Long-Term Effects of Indapamide: Final Results of a Two-Year Italian Multicenter Study in Systemic Hypertension

Gastone Leonetti, MD, Alessandro Rappelli, MD, Antonio Salvetti, MD, and Luigi Scapellato, MD

To evaluate the antihypertensive efficacy and tolerability of a low-dose diuretic, indapamide, 2.5 mg once daily, was given to 248 patients with uncomplicated, mild to moderate hypertension for a period of 24 months. Blood pressure during sitting was 165 ± 1/105 ± 1 mm Hg (mean ± standard error of the mean) at the end of the placebo run-in period and 143 ± 1/88 ± 1 and 140 ± 1/85 ± 1 mm Hg after 2 and 24 months, respectively; heart rate was clinically unmodified (from 77 ± 1 to 75 ± 1 beats/min). Total cholesterol, high-density cholesterol and serum triglycerides were unchanged, and uric acid increased significantly (from 292.0 ± 6.5 to 377.7 ± 56.5 μmol/liter). A mild reduction in serum potassium (−0.36 ± 0.03 mmol/liter) was observed after 2 and 6 months of therapy; however, the degree of reduction appeared to be lower than that from reported studies with other thiazide diuretics. The incidence of hypokalemia (serum potassium <3.5 mmol/liter) was highest in northern Italy (17%), intermediate in the central region (14%) and lowest in southern Italy (2%), although the absolute reduction in serum potassium was similar in all the geographic areas. Blood glucose tolerance was unchanged despite the changes in serum potassium. The tolerability was good on the whole, with a tendency toward an improvement in the well-being of patients, most of whom were already asymptomatic before starting the study.

(Am J Cardiol 1990;65:67H–71H)

From the Istituto di Clinica Medica Generale e Terapia Medica, Università di Milano; Istituto di Patologia Medica e Metodologia Clinica, Università di Ancona; Cattedra di Terapia Medica Sistematica, Clinica Medica I, Università di Pisa; and Divisione Medicina e Centro per lo Studio e Terapia Ipertensione, Ospedale Umberto I, Siracusa, Italy.

Address for reprints: Professor Gastone Leonetti, MD, Centro Fisiologia Clinica e Ipertensione, Via F. Sforza 35, 20122 Milano, Italy.

In a previous publication,[1] we have reported the preliminary results on tolerability and well-being of patients with mild to moderate hypertension during 1 year of treatment with indapamide. Since then, we have completed the study, which was scheduled for a 2-year period, and this report presents the final results. The longer duration of the study allows for a better evaluation of the time course of the antihypertensive efficacy of this agent and its impact on serum electrolytes, lipoproteins, and blood sugar tolerance as well as subjective tolerability. It is generally accepted that untreated arterial hypertension is one of the major cardiovascular risk factors,[2,3] and if blood pressure reduction is achieved there is a significant decrease in many, but not all, cardiovascular events, as shown in epidemiologic trials of the Veterans Administration Study,[4] Australian Study,[5] Medical Research Study[6] and the European Study in Elderly Hypertensives.[7] The minor reductions in coronary heart events in contrast to those in cerebrovascular and renal events or congestive heart failure have been hypothesized to be due to changes in lipoproteins (an increase in total cholesterol, low-density lipoproteins and triglycerides, and a decrease in high-density lipoproteins [HDL]), serum electrolytes (a decrease in serum potassium and probably serum magnesium), and finally a reduced blood glucose tolerance. These metabolic changes are mainly, or almost exclusively, associated with the use of thiazide diuretics.[8,9] This Italian multicenter study was performed with indapamide, a diuretic agent which alone or in combination has been shown to be equivalent to other antihypertensive agents.[10,11] Indapamide was selected because of its pharmacokinetic characteristics (only 5% of the drug is excreted in the urine),[12] higher concentration at the vascular wall,[12] and pharmacodynamic properties (increased production of renal prostaglandin)[13] that reduce blood pressure with minimal diuretic activity.

METHODS

This Italian multicenter study (31 centers) followed up patients over a 2-year period. Three hundred forty-two patients of both genders, age range 19 to 77 years (mean ± standard error of the mean 50.32 ± 0.52), and a sitting diastolic blood pressure between 95 and 115 mm Hg after a 1-month placebo run-in period, and with no contraindications to the use of diuretics or β blockers, were admitted to the study and received a single daily administration of indapamide, 2.5 mg. If, after 1 month of indapamide treatment, the sitting diastolic blood pressure was reduced ≥5 mm Hg, patients continued to receive indapa-

TABLE I Questionnaire Evaluating the Incidence and Severity of Adverse Effects and Well-Being

Self Evaluation	
Mood	
Physical activity	By visual scale
Physical health	
Alertness	
Checklist of 19 Items	
	Possible answers
Sadness	
Headache	
Sweating	
Cough	Often/rarely/never
Nasal obstruction	
Shortness of breath	
Cold extremities	
Dizziness	
Intestinal dysfunction	
Sleep dysfunction	
Skin rashes	
Unsteadiness	
Tiredness	Yes/No
Faintness	
Nocturia	
Sexual activity	
Physical activity	
Feeling unwell	
Nausea	

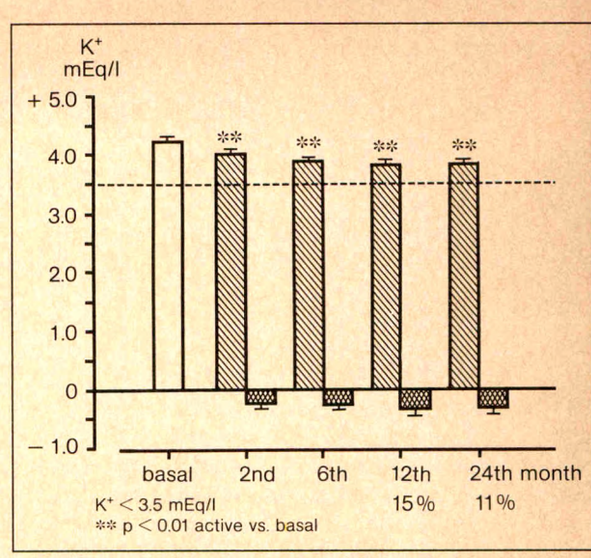


FIGURE 2. Serum potassium during indapamide, 2.5 mg once daily, monotherapy for 24 months in hypertensive patients. Values are expressed as means ± standard error of the mean. *Open bar*, pretreatment; *slashed bar*, during active treatment; *dotted line*, lower value of normal range; *bars below the abscissa*, mean ± standard error of the mean reductions vs pretreatment; **p <0.01 active vs pretreatment.

mide therapy for a further period of 1 month (responders), whereas the other patients were withdrawn from the study (nonresponders). If the diastolic blood pressure in the responders was still >95 mm Hg after 2 months of indapamide therapy, 100 mg of atenolol was added, whereas the patients with a diastolic blood pressure <95 mm Hg continued to receive only indapamide. The blood pressure was measured with a mercury sphygmomanometer after 5 minutes of rest in the seated position: systolic blood pressure was measured at the start and diastolic blood pressure was measured at the end (phase V) of Korotkoff sounds. The blood pressure registered was the average of 3 measurements taken at 2- to 3-minute intervals. The incidence of adverse effects and the evaluation of well-being were investigated by means of a checklist and a self-administered questionnaire (Table I). The patients were seen monthly during the first 6 months of the study and at 3-month intervals thereafter in the outpatient department.

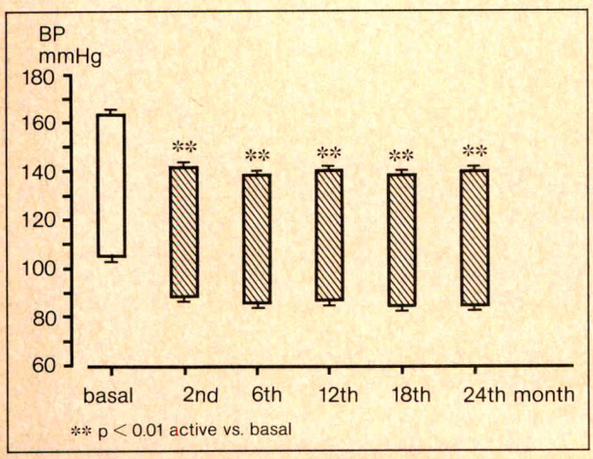


FIGURE 1. Sitting blood pressure (BP) during indapamide, 2.5 mg once daily, monotherapy for 24 months in patients with mild to moderate hypertension. Values are expressed as mean ± standard error of the mean. *Open bar*, pretreatment; *slashed bar*, during active treatment. All reductions are statistically significant (p <0.01).**

Blood pressure, heart rate, body weight, physical well-being, and the items on the checklist and the self-administered questionnaire were checked during each visit. Laboratory tests (hematocrit, red and white blood cell counts, serum sodium, potassium, creatinine, uric acid, total cholesterol, high-density cholesterol, triglycerides, fasting and postprandial glucose, transaminases, alkaline phosphatase) and urinalysis were performed before and 2, 6, 12, 18 and 24 months after indapamide treatment.

Of the 397 patients admitted to the run-in period, 342 satisfied the admission criteria and 248 of them (72%) had a diastolic blood pressure <95 mm Hg and a reduction >5 mm Hg after 2 months of monotherapy with indapamide. The results obtained in this group treated with indapamide alone for a 2-year period are reported.

Statistical analysis: A 2-way analysis of variance (time, patients) was used. For modal variables, the Friedman or a Cochran tests were used. The statistical calculation was done on a VAX 785 (Digital Equipment Corporation).

RESULTS

Population: Of the 342 patients admitted to the study at the end of the run-in period who received indapamide, 2.5 mg once daily, as monotherapy for 2 months, 248 (72%) were responders (i.e., sitting diastolic blood pressure <95 mm Hg with a reduction of ≥5 mm Hg after treatment) and continued with the monotherapy regimen for the duration of the study. Forty-three patients (13%)

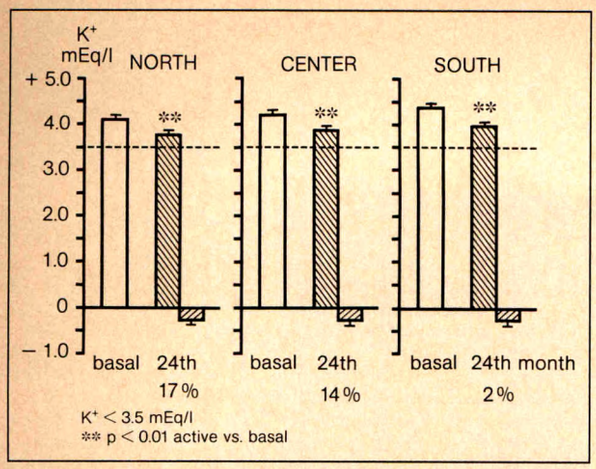


FIGURE 3. Serum potassium before and after 24 months of indapamide, 2.5 mg once daily, monotherapy in the 3 subgroups (Northern, Central and Southern Italy). Values are expressed as mean ± standard error of the mean. *Open bars,* pretreatment; *slashed bars,* after 24 months; *dotted line,* lower value of normal range; *bars below the abscissa,* absolute reduction vs pretreatment.

had a reduction in diastolic blood pressure >5 mm Hg but the diastolic values were still >95 mm Hg, and therefore these patients received atenolol 100 mg in association with indapamide during the follow-up. Forty-five patients (13%) were nonresponders and were discharged from the study, and 6 patients withdrew (5 were lost to follow-up and 1 patient died of a cause unrelated to hypertension and its treatment).

Of the 248 patients who received indapamide, 2.5 mg monotherapy, 186 (75% of the responders after 2 months or 54% of the whole population admitted to the study) completed the 24 months of treatment. Of the 62 withdrawals, 54 were lost to follow-up, 3 had hypokalemia necessitating withdrawal, and another 5 discontinued for reasons unrelated to the study.

Blood pressure and heart rate: Pretreatment sitting blood pressure of the 248 patients who were treated with indapamide, 2.5 mg monotherapy, for the duration of the study was 165 ± 1/105 ± 1 mm Hg (mean ± standard error of the mean). This showed no difference from the blood pressure of the whole population who satisfied the admission criteria at the end of the run-in period: 163 ± 1/104 ± 1 mm Hg. Blood pressure was 143 ± 1/88 ± 1 mm Hg and 140 ± 1/85 ± 1 mm Hg after 2 and 24 months of treatment, respectively ($p < 0.01$) (Fig. 1).

Heart rate was 77 ± 1 beats/min before indapamide therapy and remained unchanged, with a final value of 75 ± 1 beats/min.

Serum electrolytes: Pretreatment plasma potassium was 4.21 ± 0.03 mmol/liter and was significantly ($p < 0.01$) reduced after 2 months of indapamide therapy to 3.99 ± 0.03 mmol/liter (mean −0.22 ± 0.03 mmol/liter); only a minor further reduction was found thereafter (3.87 ± 0.03 mmol/liter) after 24 months: −0.12 ± 0.03 mmol/liter when compared with the second month of treatment (Fig. 2). A serum potassium level <3.5 mmol/liter was found in 15% of the patients after 12 months and in 11% after 24 months of therapy. According to the doctor's judgment, oral potassium could be added during treatment with indapamide.

When the results were analyzed in terms of the geographic area of the patients, we found that pretreatment serum potassium levels were higher in the southern part of Italy (4.30 ± 0.05 mmol/liter), intermediate in the central region (4.21 ± 0.03 mmol/liter) and lower in the northern part (4.10 ± 0.05 mmol/liter). After similar reductions in serum potassium in all 3 subgroups during indapamide treatment (between −0.32 and −0.38 mmol/liter), the final potassium levels were lower, and on the contrary, the incidence of serum potassium ≤3.5 mmol/liter was now higher in the northern population than in the southern and central populations (Fig. 3).

The level of plasma sodium was unmodified for the duration of the study (Table II).

Serum lipoprotein (Table II): Average total cholesterol and HDL cholesterol were unchanged during indapamide therapy. Changes >0.77 mmol/liter for total cholesterol were found in 22 patients (11 patients had an increase and 11 a decrease). An increase or decrease >0.26 mmol/liter for HDL cholesterol was observed in a few patients (4 and 5, respectively). Average serum triglycerides were unchanged and again only a few patients had changes in either direction >0.22 mmol/liter.

Blood glucose: Average fasting and postprandial blood sugar were unmodified during long-term treatment

TABLE II Plasma Concentrations of Creatinine (μmol/liter), Uric Acid (μmol/liter), Sodium (mmol/liter), Total and High-Density Lipoprotein Cholesterol Levels (mmol/liter), and Triglycerides (mmol/liter) Before and During 24 Months of Indapamide Monotherapy

		Months				
	Basal	2	6	12	18	24
Creatinine	80.44 ± 0.88	82.21 ± 0.88	82.21 ± 0.88	82.21 ± 1.76	83.09 ± 1.76	82.81 ± 0.88
Uric Acid	292.05 ± 6.54	377.69 ± 56.51	322.97 ± 5.91	318.81 ± 6.54	323.57 ± 6.54	317.62 ± 5.35
Sodium	139 ± 1	139 ± 1	138 ± 1	138 ± 1	138 ± 1	138 ± 1
Total cholesterol	5.51 ± 0.08	5.61 ± 0.10	5.61 ± 0.08	5.58 ± 0.08	5.51 ± 0.08	5.53 ± 0.08
HDL cholesterol	1.24 ± 0.02	1.21 ± 0.02	1.27 ± 0.02	1.27 ± 0.02	1.24 ± 0.02	1.27 ± 0.02
	48 ± 1	47 ± 1	49 ± 1	49 ± 1	48 ± 1	49 ± 1
Triglycerides	1.51 ± 0.05	1.52 ± 0.05	1.54 ± 0.04	1.59 ± 0.05	1.59 ± 0.04	1.51 ± 0.04
	134 ± 5	135 ± 5	137 ± 4	141 ± 5	141 ± 4	134 ± 4

Values are mean ± standard error of the mean.

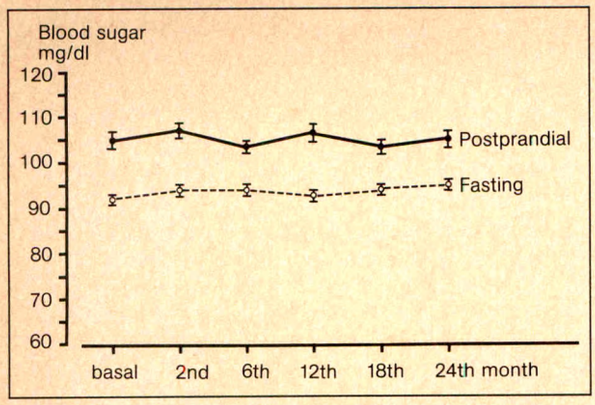


FIGURE 4. Fasting and postprandial blood glucose before and during 24 months of indapamide, 2.5 mg once daily, monotherapy. *Dashed line*, fasting; *solid line*, postprandial glucose. Values are expressed as mean ± standard error of the mean.

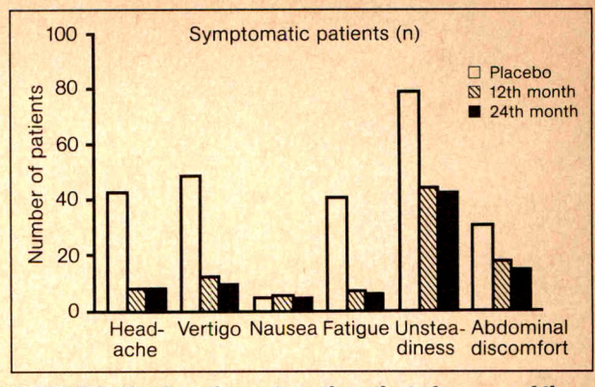


FIGURE 5. Number of symptomatic patients for some of the most frequently reported adverse effects before (*open bars*) and after 12 (*slashed bars*) and 24 months (*filled bars*) of indapamide, 2.5 mg once daily, monotherapy.

with indapamide (Fig. 4): only 2 patients had an increase and 2 a decrease in blood glucose >1.11 mmol/liter.

Serum uric acid (Table II): Serum uric acid significantly increased during long-term indapamide therapy with a peak after 2 months of therapy (from 292.0 ± 65 to 377.7 ± 56.5) and lower values thereafter.

Tolerability and well-being: The tolerability of indapamide treatment was evaluated by means of a checklist including 19 items and a self-assessment questionnaire to evaluate mood, physical feeling, activity and alertness (Table I). In all, there was an improvement, or no change, in the symptoms evaluated from the checklist during active treatment. The number of patients who complained of adverse effects was lower during indapamide therapy than during the run-in period (Fig. 5). The physical well-being, assessed from 19 items of the checklist, was unchanged in 79%, improved in 15% and worsened in 6%; the sense of well-being was unmodified in 64%, improved in 25% and worsened in 11%. Sexual function was unchanged in 88% and improved in almost all the remaining patients. The improvement was maximal during the first year of treatment; however, patients who were withdrawn from the study or lost to follow-up were not included in the analysis and this may falsely improve the results.

DISCUSSION

In this Italian multicenter study, we have investigated the antihypertensive efficacy, the impact on serum electrolytes, lipoproteins and blood glucose tolerance, and finally the influence on well-being of indapamide, 2.5 mg once daily, as monotherapy. To achieve this aim, we have admitted to the study only patients with mild and moderate arterial hypertension (who represent most of the hypertensive patients), and for ethical reasons only patients classified as responders (i.e., patients attaining a sitting diastolic blood pressure <95 mm Hg and a reduction >5 mm Hg after 2 months of therapy) were followed-up for 24 months.

The antihypertensive efficacy of indapamide, 2.5 mg once daily, in our population of mild and moderate hypertensive patients was satisfactory. After 2 months of treatment, 72% of the patients admitted to the study were classified as responders, according to the criteria of our study, and this result is in agreement with that reported in 2 other multicenter studies.[14,15] The percentage of responders still remains >60% if we select diastolic blood pressure <90 mm Hg as a more strict criterion for the definition of "responders." The percentage of responders was lower at the end of the 24 months of therapy (54% of the whole population admitted to the study), but the difference between the values after 2 and 24 months is predominantly due to the fact that 54 patients were lost to follow-up. Although we do not know the specific reasons that induced these patients to abandon the study, it seems unlikely that a treatment failure was the main cause, because blood pressure was consistently reduced for the duration of the study in the patients defined as responders after 2 months of therapy and regularly followed up thereafter (Fig. 1). The blood pressure reductions observed after 2 and 24 months were −20/−17 and −23/−20 mm Hg, respectively.

As expected, because of the pharmacodynamic action of diuretics, indapamide caused a reduction in the serum potassium level, which was 0.34 ± 0.03 mmol/liter in our patients, almost maximal after 2 months of treatment and only slightly greater thereafter. The reduction in serum potassium during long-term treatment with indapamide was lower than that reported with the other diuretics, apart from potassium-sparing agents. However, diuretics were previously prescribed at doses higher than currently recommended. In our study, the final percentage of patients with serum potassium levels <3.5 mmol/liter was 11%. Three patients were withdrawn because of a reduction in serum potassium levels considered dangerous by their physicians. In another patient the serum potassium level was <3.0 mmol/liter. The significance of the reduction in plasma potassium differed in the 3 different geographic areas of the country: The pretreatment average plasma potassium level was lowest in the northern part of Italy, intermediate in the central part, and highest in the southern part of the country. Because of the different pretreatment levels, the same average reduction in plasma potassium level resulted in a greater percentage of patients with a plasma potassium level <3.5 mmol/liter in the northern part of Italy compared with the other regions. Also, the reduction in plasma potassium levels caused by indapamide was already evident and maximal

during the first 2 months of treatment, whereas no further significant reductions were found thereafter. The different levels of pretreatment plasma potassium are probably attributable to different dietary habits. Plasma sodium levels did not change significantly.

In the present study, in accordance with other reports,[16,17] no significant changes occurred in total cholesterol, HDL cholesterol and serum triglycerides. Mild changes in both directions were present in only a few patients. Conversely, there was an increase in the level of uric acid, which reached a maximum after 2 months of treatment and was slightly lower thereafter.

Fasting and postprandial blood glucose levels were unchanged during treatment with indapamide and only minor and clinically irrelevant changes were observed in a few patients. The absence of significant changes in blood glucose during long-term treatment with indapamide is in agreement with other studies in diabetic[18,19] and nondiabetic[20,21] hypertensive patients. The lack of diabetogenic effect of indapamide may possibly be due to minor reduction in serum potassium or a protective action on carbohydrate metabolism resulting from the differences in the molecular structure of indapamide compared with other diuretics (many oral antidiabetic agents have a common sulfonylurea structure).

Although we cannot exclude that our data might be biased by a sequential effect, the tolerability and well-being of long-term monotherapy with indapamide, evaluated by a checklist of 19 items and self-assessment of physical fitness, was good on the whole. In our population of patients with predominantly asymptomatic mild or moderate hypertension, there was no significant worsening and possibly a tendency toward an improvement of symptoms and a positive sense of well-being.

In conclusion, our study with indapamide as monotherapy in hypertensive patients shows that blood pressure control was obtained in 75% of the patients who were responders to indapamide monotherapy after 2 months and were therefore eligible for the monotherapy follow-up of 24 months. This blood pressure control is associated with (1) a good tolerance and a trend toward an improvement in well-being; and (2) a biochemical pattern characterized by a slight increase in uric acid, a mild decrease in plasma potassium, and no changes in serum lipids and glucose tolerance.

REFERENCES

1. Leonetti G, Rappelli A, Salvetti A, Scapellato L. Tolerability and well-being with indapamide in the treatment of mild-moderate hypertension. *Am J Med 1988;84:suppl 1B:59–64.*

2. Kannel WB, Dawber TR, Kagan A. Factors in the development of coronary heart disease: six year follow-up experience. *Ann Intern Med 1961;55:33–60.*

3. Kannel WB, Dawber TR. Hypertension cardiovascular disease: The Framingham study. In: Onesti G, Kim KE, Moyer JH, eds. Hypertension Mechanism and Management. *New York: Grune & Stratton, 1973;93–110.*

4. Veterans Administration Cooperative Study Group on Antihypertensive Agents: effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *JAMA 1970;213:1143–1152.*

5. Australian Therapeutic Trial in Mild Hypertension: a five year controlled drug trial. *Lancet 1980;1:1261–1267.*

6. Medical Research Council Working Party on mild hypertension. Coronary heart disease in Medical Research Council trial of treatment of mild hypertension. *Br Heart J 1988;59:364–378.*

7. Amery A, Brixko P, Clement D, De Schaepdryver A, Fagard R, Forte J, Henry JF, Leonetti G. O'Malley K, Strasser T, Birkenhager W, Bulpitt C, Deruyttere M, Dollery C, Forette F, Hamdy R, Joossens JV, Lund-Johansen P, Petrie J, Tuomilehto J, Williams B. Mortality and morbidity results from the European Working Party on high blood pressure in the elderly trial. *Lancet 1985;1:1349–1354.*

8. Goldmann AI, Steele BW, Schnaper HW, Fitz AE, Frolich ED, Perry MH. Serum lipoproteins during chlorthalidone therapy. *JAMA 1980;244:1691–1695.*

9. Ames RP, Hill P. Raised serum lipid concentration during diuretic treatment of hypertension: a study of predictive indexes. *Clin Sci Mol Med 1978;55:311s–314s.*

10. Anavekar NA, Ludbrooke A, Louis WJ, Doyle AE. Evaluation of indapamide in the treatment of hypertension. *J Cardiovasc Pharmacol 1979;1:389–394.*

11. Houde M, Carriere S. Efficacy of indapamide in monotherapy or with beta-blocker in the treatment of moderate hypertension. *Curr Med Res Opin 1983;8:suppl 3:68–76.*

12. Campbell DB, Taylor AR, Hopkins YW, Williams JRB. Pharmacokinetics and metabolism of indapamide: a review. *Curr Med Res Opin 1977;5:suppl 1:13–24.*

13. LeBel M, Grose JH, Belleau LJ, Langlois S. Effects of indapamide on renal prostaglandin production in hypertensive patients. *Curr Med Res Opin 1983; 8:suppl 3:81–86.*

14. Abbou CB. Efficacy and tolerance of indapamide in essential hypertension. *Curr Med Res Opin 1985;9:494–497.*

15. Mimran A, Zambrowski JJ, Coppolani T. The antihypertensive action of indapamide: results of a French multicenter study of 218 ambulant patients. *Postgrad Med J 1981;57:suppl 2:60–63.*

16. Gerber A, Weidmann P, Bianchetti MG, Ferrier C, Laederach K, Mordasini R. Serum lipoproteins during treatment with the antihypertensive agent indapamide. *Hypertension 1985;7:suppl II:164–169.*

17. Meyer-Sabellek W, Gotzen R, Heltz J, Arntz HR, Schulte KL. Serum lipoprotein levels during long term treatment with indapamide. *Hypertension 1985;7:suppl II:170–174.*

18. Roux P, Courtois H. Blood sugar regulation during treatment with indapamide in hypertensive diabetics. *Postgrad Med J 1981;57:suppl 2:70–72.*

19. Osei T, Holland G, Falko JH. Indapamide. Effects on apoprotein, lipoprotein, and glucoregulation in ambulatory diabetic patients. *Arch Intern Med 1986; 146:1973–1977.*

20. Ferrara LA, Giumetti D, Fasano ML, Soro S, Iannuzzi A, Strazzullo P, Mancini M. Once-a-day indapamide therapy in hypertension. Effects on the heart and peripheral arterial circulation. *Jpn Heart J 1983;24:731–737.*

21. Royer RJ. Progress in the treatment of hypertension: a multicentre study of indapamide in 442 patients. *Curr Med Res Opin 1977;5:suppl 1:151–156.*

ADDITIONAL PARTICIPANTS

The following is a list of those who participated in the Indapamide Italian Multicenter Study, with their respective cities or towns in parentheses: G. P. Benetti, M. Fossati, A. Castelnuovo (Merate); S. Boni, S. Cosentini, A. Meani (Cassano d'Adda); M. Lombardo, V. Colloca, M. Reitani (Niguarda, Milano); G. Mariotti, C. Alli (Cinisello Balsamo); C. Mazzola, M. Meregalli, M. Valsecchi (Casatenovo); A. Monteverde, P. Occhipinti, M. Minola (Carità, Novara); C. Pasotti, A. Capra, P. Gandolfi (Voghera); E. Marras, M. G. Deledda (Oristano); M. Pittalis (Nuoro); M. Rimini, C. Fonnesu (Alghero); P. L. Cella, M. Lunardi (Barga); P. Innocenti, M. Iardella, P. Pambiaco (Carrara); A. Carnicelli, N. Giomi, R. Lenzi (Cecina); A. Bini, V. Mazzoni, S. Mainardi (Empoli); S. Ambrosoli, A. Caiaza, F. Ghisoni (Fidenza): P. D. Ricci, F. Ricci (Lucca); A. Pesola, G. Cosentino (Viareggio); L. Lucentini, M. Errico, M. Freda, F. Puzzolante (S. G. Rotondo); P. Saba, F. Giuntoli, A. Scalambrino (Pescia); G. Federigi, R. Pacini (Pistoia); E. Pallone, E. Ferrari, L. Rossi (Piombino); G. Pagni, R. Coretese (Sarzana); G.C. Saba (Seravezza); L. Papi, C. Sighieri, G. Castello (Volterra); M. Lera, P. Locci (Camaiore); C. Del Prato, S. Gramenzi, N. Lecis (La Spezia); S. Bonaventura, C. Incontro (Lentini); F. Briguglio, E. Briguglio (Messina); I. Ottaviano, S. Burrafato (Ragusa); A. Pittera (Catania); V. Rosano, B. Milano (Vibo V.)

Diuretics and the Treatment of Systemic Hypertension

Pedro Aranda, MD, and Eduardo Lopez de Novales, MD

Diuretics are still among the most frequently used antihypertensive drugs in the treatment of hypertension. Their pharmacologic and hemodynamic properties are based on the water and salt metabolism in the pathophysiology of high blood pressure. Initially, there is a reduction of plasma and extracellular fluid volume; cardiac output also decreases. After this early phase, cardiac output returns to normal with an accompanying decrease in peripheral resistance so as to correct the underlying hemodynamic fault of the hypertensive state. Diuretics have a high therapeutic efficacy either as monotherapy or in combination with β blockers, angiotensin-converting enzyme inhibitors or calcium antagonists.

The main problem with the use of diuretics is related to their metabolic side effects, which are dose-related. Currently, there is a tendency to administer low-dose diuretics, which result in fewer clinical and metabolic side effects, but with a continued antihypertensive efficacy. Therefore, low doses of diuretics can be recommended as initial therapy in the stepped-care approach of hypertension.

(Am J Cardiol 1990;65:72H–76H)

From the Hypertension Unit, Regional Hospital, Malaga, Spain.

Address for reprints: Pedro Aranda, MD, Hypertension Unit, Regional Hospital, Malaga, Spain.

Since their introduction in clinical practice in 1957[1] to the present day, diuretics have been the most frequently used antihypertensive agent.[2] Both the first therapeutic recommendations from the World Health Organization committee of experts[3] and the latest recommendations of the Joint National Committee on Detection, Evaluation, and Treatment of Hypertension in 1988[4] have consistently proposed diuretics as the hypertensive drugs of choice.

Recently, it has been argued that changes are needed in the conventional antihypertensive therapeutic approach of using diuretics and β blockers, mainly due to the possible negative biochemical effects and clinical intolerance of these agents.[5]

Faced with this prospect, the reasons for considering diuretics as the antihypertensives of choice (Table I) and their related negative clinical-biochemical effects should be examined.

EPIDEMIOLOGIC AND PHYSIOPATHOLOGIC ROLE PLAYED BY SODIUM IN THE DEVELOPMENT AND PERSISTENCE OF HIGH BLOOD PRESSURE

From an epidemiologic standpoint, there appears to be a direct relationship between the consumption of sodium and the prevalence of high blood pressure.[6] This relationship between sodium chloride and blood pressure has recently been demonstrated by the Intersalt Cooperative Research Group.[7] These results indicate that the urinary excretion of sodium is significantly related to blood pressure regardless of body mass ratio and alcohol intake.

However, despite the difficulties encountered in conducting studies on the role of sodium restriction in the reduction of blood pressure, several investigators[7–9] concluded that sodium dietary restriction leads to a short- and long-term decrease in blood pressure in hypertensive patients. There appears to be great heterogeneity in the response of blood pressure to the intake and to the depletion of sodium. Two clearly different population subgroups exist, a sodium-sensitive one that responds to changes in the intake of sodium and a sodium-resistant one that does not.[6,10]

These clinical epidemiologic considerations on the role of sodium intake in the development and persistence of high blood pressure are based on physiopathologic aspects. They focus on the role played by sodium as a result of a deficient renal excretion, a disturbance in the transmembrane ion transport, or an increase in peripheral vascular resistance.[11,12] Thus, in a salt-sensitive population, an increase in the intake of sodium chloride would lead to an increase in peripheral vascular resistance and

TABLE I Advantages for the Use of Diuretics as Initial Antihypertensive Therapy

Epidemiologic and physiopathologic role of sodium in the pathogenesis of high blood pressure
Hemodynamic and pharmacologic effects
Therapeutic efficacy
Good compliance
Relatively inexpensive

blood pressure. The increase in both sodium and intracellular calcium leads to vascular reactivity and to an increase in sympathetic activity which, apart from increasing the peripheral vascular reactivity, would lead to a blockade in the renal excretion of sodium (Fig. 1).

ANTIHYPERTENSIVE PHARMACOLOGIC AND HEMODYNAMIC EFFECTS OF DIURETICS: THERAPEUTIC EFFICACY

Hemodynamically, diuretics decrease blood pressure initially by reducing the volume of extracellular fluid and cardiac output with a compensatory increase in peripheral vascular resistance. However, in the medium to long term, cardiac output tends to normalize. This depends on the diuretic dosage and the sustained decrease in peripheral vascular resistance,[13,14] which is the major physiopathologic factor in the maintenance of the hypertensive state. Although the mechanisms that maintain a low peripheral vascular resistance are not completely defined, the vasodilating action of diuretics (Fig. 2) appears to be directly mediated by a reduction in vascular reactivity, a secondary effect of the decrease in the intracellular level of sodium and calcium in the smooth muscle cells of the vascular wall,[14–16] or indirectly by reducing the vasoconstricting response of arterioles to the action of endogenous vasoconstricting stimuli (catecholamines, angiotensin, actomyosin) or promoting the synthesis of vasodilating substances, such as prostacyclin or kallikreins.[13–17] Alternatively, the same adjustment that normalizes cardiac output, by self-regulation of tissues, may be responsible for the sustained reduction in peripheral vascular resistance.[16]

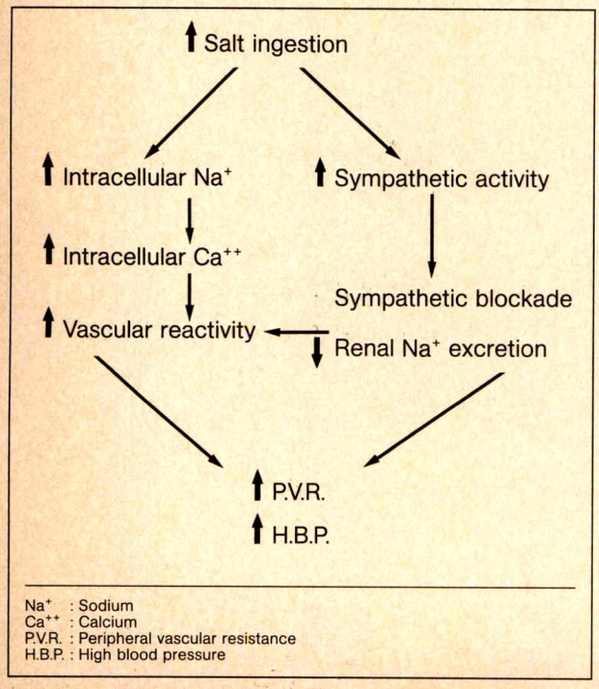


FIGURE 1. Mechanisms of increasing blood pressure in the salt-sensitive population. H.B.P. = high blood pressure; P.V.R. = peripheral vascular resistance.

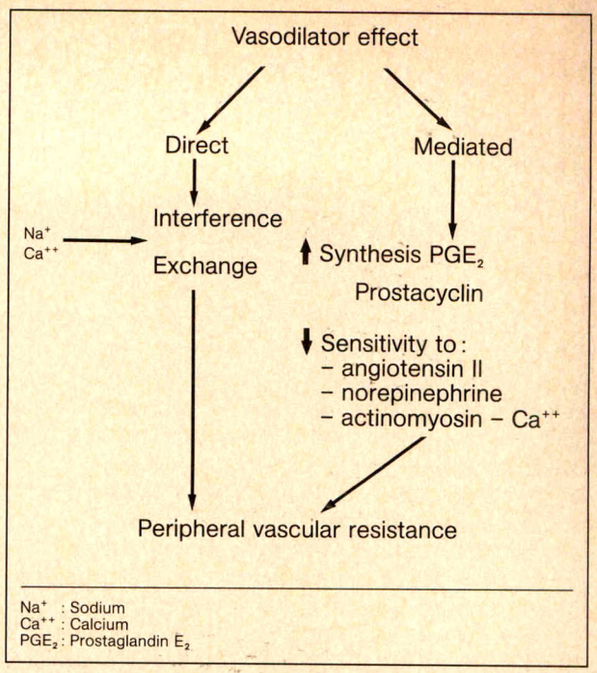


FIGURE 2. Pharmacologic antihypertensive effects of diuretics. PGE_2 = prostaglandin E_2.

Therefore, epidemiologic and physiopathologic implications of sodium in the pathogenesis of high blood pressure and the pharmacologic effects of diuretics enable us to consider these drugs as one of the antihypertensive groups of choice.

With regard to their antihypertensive response, diuretics have an efficacy similar to that of the angiotensin-converting enzyme inhibitors, calcium antagonists and β blockers in the treatment of mild to moderate hypertension and may be used as monotherapy or in combination with the other hypertensive agents.[17–19] Moreover, diuretics may help to counteract in many patients the hypertensive effects of a high salt intake or the concurrent use of sodium-retaining drugs, such as nonsteroidal anti-inflammatory drugs,[13] and to prevent the water and salt retention that may be produced by some vasodilators such as hydralazine or minoxidil.[13,16,17]

With the exception of hypertensive situations complicated by edematous states or kidney failure, or those that require a rapid volume depletion, for which loop diuretics might be chosen, thiazide diuretics are preferable for the treatment of uncomplicated hypertension.[13,17]

Opposed to loop diuretics, thiazide diuretics have been shown to produce a flat dose-response curve, and their antihypertensive efficacy does not improve significantly

TABLE II Factors Influencing the Effects of Diuretics on the Renal Management of Potassium and Magnesium

Type of diuretic
Dose
Duration of treatment
Degree of salt restriction
Normal balance of potassium and magnesium
Associated diseases: left ventricular hypertrophy, ischemic heart disease

when the dose is increased.[13,17,20,21] High doses of diuretics trigger a series of reflex-type mechanisms, such as sympathetic hyperactivity and activation of the renin-aldosterone-angiotensin system, in response to the excessive loss of water and salt.[13,17,22-24] Nevertheless, this is not a general response, because in some patients a direct correlation has been described between volume loss and reduction of blood pressure after the use of thiazides.[25]

Therefore, the current trend in the use of diuretics for treating uncomplicated hypertension is to give thiazides at low doses because of their high therapeutic efficacy.

Spironolactone and potassium-sparing diuretics (triamterene or amiloride) have a very mild antihypertensive action,[17] so they tend to be used only in combination with a thiazide or loop diuretic to prevent subsequent potassium loss. Nevertheless, the use of low doses of thiazides is associated in most patients with a mild potassium loss which may be counteracted, without the need for additional distal-acting diuretics, by a diet with moderate salt restriction and a potassium-rich intake.[13,17,26]

Apart from the excellent results obtained with the use of diuretics as monotherapy for the treatment of mild to moderate essential hypertension, especially in blacks and the elderly, they provide an excellent adjuvant to other antihypertensive agents.[4,19] Lower doses of diuretics are required when they are used in combination with β blockers,[18,27] angiotensin-converting enzyme inhibitors[18,28] and calcium antagonists[29] because of the increased therapeutic efficacy. This may also improve the clinical tolerance of diuretics.[28,30]

DISADVANTAGES OF DIURETICS

The problems derived from the use of diuretics in the treatment of hypertension are related to their clinical tolerance and to the negative metabolic effects on uricemia, serum potassium levels and lipid or carbohydrate metabolism.[13,15,17,31,32]

Most clinical and biochemical side effects are dose dependent and can be minimized by reducing the dose of these drugs.[13,17,20,30,32] The most frequently observed adverse effects (>1%) include gastrointestinal disturbances (vomiting, nausea, diarrhea), weakness, dizziness, skin rash, sexual dysfunction and impotence, and muscle cramps.[31,33,34] Excessive doses of diuretics or their use in patients prone to volume depletion, such as the elderly or patients with disturbed sympathetic reflexes, may cause orthostatic hypotension.[14,31] Apart from the dose, other factors that lower clinical tolerance are old age[35] or the presence of associated pathologic conditions, such as gout, dysfunction of the prostate and diabetes mellitus.

Most metabolic side effects induced by diuretics are the result of varying degrees of volume contraction after water and salt depletion.[36] These can be minimized to a great extent by the use of low doses.[13,17,20,30,36]

The most important negative metabolic effects attributable to antihypertensive treatment with diuretics is their arrhythmia-induced potential as a result of hypokalemia and hypomagnesemia.[32,37,38] Physiopathologically,

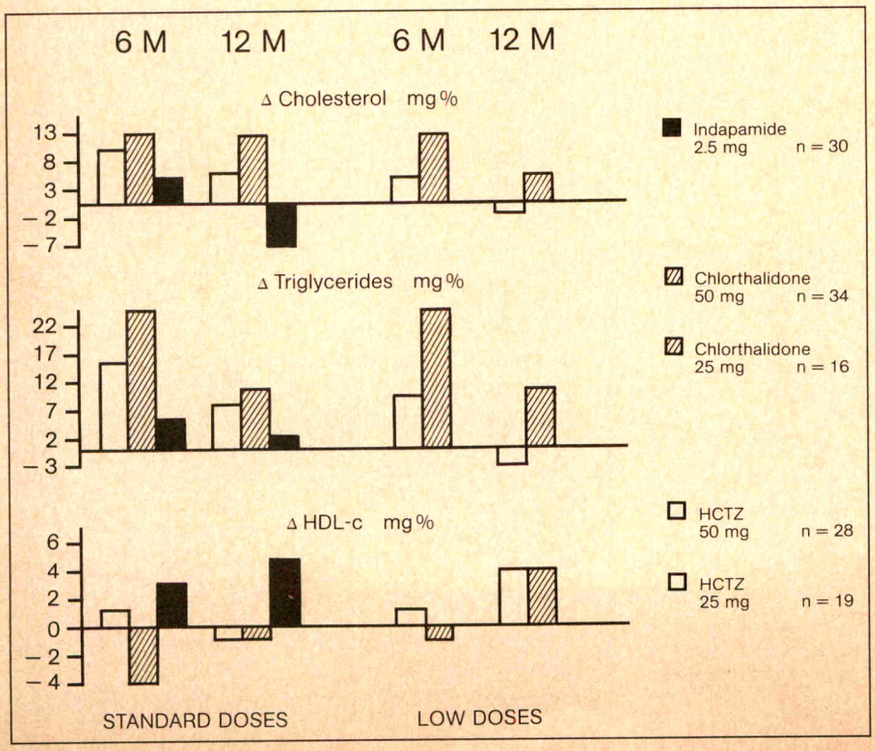


FIGURE 3. Lipid profile modification with standard and low doses of different diuretics. HCTZ = hydrochlorothiazide; HDL-c = high-density lipoprotein cholesterol; M = month.

hypokalemia is the result of the urinary loss of sodium and potassium and of the activation of the angiotensin-renin system induced by volume contraction.[36] The arrhythmogenic effect of hypokalemia, increased by the loss of magnesium,[31,39] seems to be related both to an increased sympathetic activity[31] and to an increase in the irritability of myocardial tissue due to changes in the intracellular/extracellular potassium ratio.[26]

The concern over diuretic-induced hypokalemia has recently been questioned.[40,41] A controversy exists about the role of diuretic-induced hypokalemia in the development of arrhythmias; some studies suggest an increased risk,[37,38,42] while others have failed to confirm it.[43–45]

Although the initial results of the Multiple Risk Factor Intervention Trial[46] showed a greater mortality in the subgroup of patients with high blood pressure and electrocardiographic abnormalities treated with diuretics, neither the final report of the Medical Research Council[47] nor The Hypertension Detection and Follow-Up Program[48] observed any adverse effects of diuretic therapy on the cardiovascular mortality of patients. Moreover, the arrhythmogenic action of diuretics is likely to be directly related to their protracted use, particularly in prone persons, such as those with ischemic disease,[22,41] basal electrocardiographic disturbances[46] or left ventricle hypertrophy.[31,37,40]

In contrast, the potassium losses caused by diuretics may be minimized by using low doses,[13,17,26,39,40] reducing sodium intake and increasing potassium intake,[13,17,26,31] or adding potassium-sparing distal diuretics (Table II).

Diuretics may lead to glucose intolerance or trigger the onset of diabetes, especially in obese persons or those with a family history of diabetes.[17,47] Physiopathologically, this appears to be related to the suppression of the pancreatic release of insulin induced by hypokalemia,[49] and there is evidence that these effects can be prevented by maintaining suitable levels of potassium.[26] Clinically, hyperglycemia usually appears with long-term use and disappears when treatment is discontinued.[17] Although there is no evidence that these disorders of carbohydrate metabolism can increase the vascular risk of hypertensive patients, the blood sugar levels of hypertensive patients treated with diuretics should be regularly checked.

Although the prevalence of hyperuricemia in non-treated hypertensive patients is high, it is even greater after the use of diuretics, as a result of an excessive volume contraction.[17,36] Treatment is not required, except in susceptible patients, or in those with plasma levels of uric acid in excess of 65 μmol/liter in women or 77 μmol/liter in men.[17]

Finally, increases in triglycerides, total cholesterol and low-density lipoprotein and very low density lipoprotein cholesterol fractions have been described with the use of diuretics, mainly thiazides,[17,50,51] furosemide, xipamide, bumetanide, metolazone or pyretanide.[50,51] These changes in the lipid profile are quantitatively variable, dose-dependent,[13,17,50–52] and physiopathologically related to a greater sympathetic activity, release of catecholamines,[50] and to a reactive hyperinsulinism, to compensate for the increase in glucose after the increase in growth hormone.[50,52] Indapamide, a diuretic classified as an indoline, with a mechanism and place of activity apparently similar to the thiazides,[50] does not seem to cause any negative changes in the lipid profile,[50,53,54] even in hypertensive patients with hypercholesterolemia[55] (Fig. 3). The effects of diuretics on lipids tend to decline on a long-term basis[31,34,40] or when they are discontinued.[51] The clinical effect on the vascular morbidity and mortality of hypertensive patients with all these lipid changes, generally within a normal range,[40] needs to be determined.

In conclusion, because of the epidemiologic and physiopathologic implications of sodium in the development and persistence of hypertension, and the vasodilating hemodynamic effects, high therapeutic efficacy, minimal clinical and biochemical side effects, relatively low cost and, in general, good compliance, low doses of diuretics should continue to be considered as antihypertensive agents of choice.[36,40]

REFERENCES

1. Hollander W, Wilkins RW. Chlorothiazide: a new type drug for the treatment of arterial hypertension. *Boston Med Q 1957;8:68–75.*

2. Ray WA, Schaffner W, Oates JA. Therapeutic choice in the treatment of hypertension. *Am J Med 1986;81:suppl 6C:9–19.*

3. W.H.O. Arterial Hypertension. *Technical Report Series, Geneva 1978;628: 36–38.*

4. The 1988 Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. *Arch Intern Med 1988;148:1027–1028.*

5. Zusman RM. In defense of alternative antihypertensive therapy. *Hypertension 1988;12:327–329.*

6. Luft FC, Weinberger MH. Sodium intake and essential hypertension. *Hypertension 1982;4:suppl III:14–19.*

7. Intersalt Cooperative Research Group. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. *Br Med J 1988;297:319—328.*

8. Morgan T, Gillies A, Morgan G, Adam W, Wilson M, Carney S. Hypertension treated by salt restriction. *Lancet 1978;1:227–231.*

9. McGregor GA, Best FE, Can JM, Markandu ND, Elder AM, Sagnella SA, Squires M. Double-blind randomized cross-over trial of moderate sodium restriction in essential hypertension. *Lancet 1982;1:351–353.*

10. Brown JJ, Lever AF, Robertson JIS, Semple PF. Should dietary sodium be reduced? The sceptic's position. *Q J Med 1984;53:427–437.*

11. Kaplan NM. Primary (essential) hypertension: Pathogenesis. In: Clinical Hypertension. 4th ed. *Baltimore: Williams & Wilkins, 1986:56–122.*

12. Garay RP, Elghozi JL, Daghar G, Meyer P. Laboratory distinction between primary and secondary hypertension by measurement of erythrocyte cation fluxes. *N Engl J Med 1980;302:769–771.*

13. Lant A. Diuretic drugs. Progress in clinical pharmacology. *Drugs 1986; 31:suppl 4:40–45.*

14. Morgan T. The use of diuretic drugs and aldosterone antagonists in hypertension. In: Doyle AE, ed. Handbook of Hypertension. vol. 5. *Amsterdam: Elsevier, 1984:67–91.*

15. Eknoyan G. The physiological basis of diuretic therapy. Non-renal cellular and metabolic effects. In: Eknoyan GE, Martinez M, Maldonado M, eds. The Physiological Basis of Diuretic Therapy in Clinical Medicine. *Orlando: Grune & Stratton, 1986;76–94.*

16. Struyker-Boucher HHJ, Smith JFM, Kleinjans JCS, Van Essen H. Hemodynamic actions of diuretic agents. *Clin Exp Hypertension 1983;5:A2:209–223.*

17. Venkata C, Ram S, Kaplan NM. Diuretic therapy in clinical medicine: Use in hypertension. In: Eknovan GE, Martinez M, Maldonado M, eds. The Physiological Basis of Diuretic Therapy in Clinical Medicine. *Orlando: Grune & Stratton, 1986;1211–224.*

18. Zanchetti A. Angiotensin converting enzyme inhibition in clinical practice. A re-examination of stepped-care: a retrospective and a prospective. *J Cardiovasc Pharmacol 1985;7:suppl 1:5126–5131.*

19. Gifford Jr RW. Essential hypertension. Cost-effective evaluation and treatment. *Am J Med 1986;81:suppl 6C:33–38.*

20. McWeigh G, Galloway D, Johnston D. The case for low dose diuretics in hypertension: comparison of low and conventional doses of cyclopenthiazide. *Br Med J 1988;297:95–98.*

21. Lant AF. Evaluation of diuretics and ACE inhibitors, their renal and antihypertensive action parallels and contrasts. *Br J Clin Pharmacol 1987;23:27–41.*

22. Cranston WI, Juel-Jensen BE, Semmence AM, Handfield Jones RPC, Forbes JA, Mutch LMN. Effects of oral diuretics on raised arterial pressure. *Lancet 1963;2:966–970.*

23. Weber MA, Lopez-Ovejero JA, Drayer JI, Case DB, Laragh JH. Renin reactivity as a determinant of responsiveness to antihypertensive treatment. *Arch Intern Med 1977;137:284–289.*
24. Vaughan DE, Carey RM, Peach MJ, Ackerly JA, Ayers CR. The renin response to diuretic therapy. A limitation of antihypertensive potential. *Circ Res 1978;42:376–381.*
25. Freis ED, Reda DJ, Materson BJ. Volume (weight) loss and blood pressure response following thiazide diuretics. *Hypertension 1988;12:244–250.*
26. Langford HG. Effect of potassium depletion by thiazides. *Arch Intern Med 1988;148:1265–1266.*
27. McGregor GA, Banks RA, Markander ND, Bayliss J, Roulston J. Lack of effect of beta-blocker in flat response to thiazide in hypertension: efficacy of low dose thiazide combined with beta-blocker. *Br Med J 1983;286:1535–1538.*
28. Aranda P, Aranda JM, Nunez D, Lopez S, Ramos JL. Captopril vs nifedipino retard en el tratamiento de la hipertension arterial essenial ligera-moderada. Resultados de un estudio ambulatorio, abierto, multicentrico. *Rev Clin Esp, in press.*
29. Zusman R, Christensen D, Federman E, Kochar M, McCarron D, Porush JG, Spitalewitz S. Comparison of nifedipine and propranolol in combination with diuretics for the treatment of hypertension. *Am J Med 1987;82:3B:37–41.*
30. Bengtsson C, Johnsson G, Sannerstedt R, Werko L. Effect of different doses of chlorthalidone on blood pressure, serum potassium and serum urate. *Br Med J 1975;1:197–199.*
31. Weinberger MH. Diuretics and their side effects. *Hypertension 1988;11:16–20.*
32. Frommer JP, Wesson DE, Eknoyan G. Side effects and complications of diuretic therapy. In: Eknoyan G, Martinez M, Maldonado M, eds. The Physiological Basis of Diuretic Therapy in Clinical Medicine. *Orlando: Grune & Stratton, 1986:293–309.*
33. Curb JD, Borhani NO, Blaszkowski TP, Zimbaldi N, Fotin S, Williams W. Long-term surveillance for adverse effects of antihypertensive drugs. *JAMA 1985;253:3263–3268.*
34. Medical Research Working Party on Mild to Moderate Hypertension. Adverse reactions to bendrofluazide and propranolol for the treatment of mild hypertension. *Lancet 1981;2:539–543.*
35. Arnold JMO, McDevitt DG. Antihypertensive drugs. In: Stout RW, ed. Arterial Disease in the Elderly. *New York: Churchill Livingstone, 1984;190–198.*
36. Kaplan NM. Management strategies in hypertension. In: Brenner BM, Stein JH, eds. Hypertension. *New York: Churchill Livingstone, 1981;350–353.*
37. McLenachan JM, Henderson E, Morris KI, Dargie HJ. Ventricular arrhythmias in patients with hypertensive left ventricular hypertrophy. *N Engl J Med 1987;317:787–792.*
38. Holland OB, Nixon JV, Kuhnert I. Diuretic induced ventricular ectopic activity. *Am J Med 1981;70:762–768.*
39. Ryan MP. Diuretics and potassium magnesium depletion. *Am J Med 1987;82:suppl 3A:38–47.*
40. Moser M. In defense of traditional antihypertensive therapy. *Hypertension 1988;12:324–326.*
41. Struthers AD. Diuretics and arrhythmias in hypertension: is there cause for concern: ACE Report 50. In: Nicholls MG, ed. *Great Britain: Gower Academic Journal, 1988.*
42. Hollifield JW, Staton PE. Thiazide diuretics, hypokalemia and cardiac arrhythmias. *Acta Med Scand 1981;suppl 647:67–73.*
43. Papademitriou V, Burris JF, Notargiacomo A, Fletcher RD, Freis ED. Thiazide therapy is not a cause of arrhythmia in patients with systemic hypertension. *Arch Intern Med 1988;148:1272–1276.*
44. Leif PD, Beligon I, Mates J. Diuretic induced hypokalemia does not cause ventricular ectopy in uncomplicated essential hypertension (abstr). *Kidney Int 1984;25:203.*
45. Madias JE, Madias NE, Gavras HP. Non-arrhythmogenicity of diuretic-induced hypokalemia. *Arch Intern Med 1984;144:2171–2176.*
46. Multiple Risk Factor Intervention Trial: Risk factor changes and mortality results. *JAMA 1982;248:1465–1476.*
47. Medical Research Council Trial of Treatment of Mild Hypertension: Principle results. Medical Research Council Working Party. *Br Med J 1985;291:97–104.*
48. The Hypertension Detection and Follow-Up Program Cooperative Research Group: The effect of antihypertensive drug treatment on mortality in the presence of resting electrocardiographic abnormalities at baseline. The HDFP experience. *Circulation 1984;70:996–1003.*
49. Effect of thiazides on carbohydrate metabolism in patients with hypertension. *N Engl J Med 1961;265:1028–1033.*
50. Lardinois CK, Neuman SL. The effects of antihypertensive agents on serum lipids and lipoproteins. *Arch Intern Med 1988;148:1280–1288.*
51. Ames RP, Hill P. Elevation on serum lipid levels during diuretic therapy of hypertension. *Am J Med 1976;61:748–757.*
52. Ames RP. Serum lipid and lipoprotein disturbances during antihypertensive therapy. *Hosp Formulary 1981;16:1476–1486.*
53. Beiling S, Vukovich RA, Neiss ES, Zisblatt M, Webb EM, Losi M. Long-term experience with indapamide. *Am Heart J 1983;106:258–262.*
54. Gerber A, Weidmann P, Branchetti MG. Serum lipoproteins during treatment with the antihypertensive agent indapamide. *Hypertension 1985;7:suppl 2:164–169.*
55. Scalabrino A, Galeone F, Giuntoli F. Clinical investigation on long-term effects of indapamide in patients with essential hypertension. *Curr Ther Res 1984;35:17–22.*

Beneficial Effects of Indapamide on Lipoproteins and Apoproteins in Ambulatory Hypertensive Patients

Isabelle Aubert, MD, Francis Djian, MD, and Jacques Rouffy, MD

Among the numerous risk factors for atherosclerosis, 2 are particularly important: hypertension and primary or secondary abnormalities of plasma lipids and lipoproteins. Antihypertensive treatments significantly decrease the risk of cerebrovascular accidents, renal failure or hypertensive cardiomyopathy, but they have little influence on coronary artery disease. It has been suggested that some antihypertensive agents may have deleterious effects by altering serum lipoproteins and this may override the benefit of blood pressure reduction. Diuretics increase the blood concentration of total cholesterol, low-density lipoproteins and triglycerides. Indapamide, a methylindoline agent with vasodilator activity, has no adverse lipid effects.

Twenty-six studies have clearly demonstrated that indapamide appears to be unique among diuretics because of an absence of adverse lipid effects. In some studies indapamide significantly increased high-density lipoprotein cholesterol, apoproteins A_1, A_2 and apoprotein E. When a thiazide diuretic had been given previously, indapamide treatment normalized the lipid and lipoprotein profiles. The reason for the lack of adverse lipid effects of indapamide is discussed. Thus indapamide, 2.5 mg once daily, is effective and safe for the control of mild to moderate hypertension, both in young and older patients. It may be an optimal diuretic for use in normolipidemic or hyperlipidemic patients, as it increases high-density lipoprotein but not low-density lipoprotein cholesterol.

(Am J Cardiol 1990;65:77H–80H)

From Saint Louis Hospital, Paris, France.

Address for reprints: Isabelle Aubert, MD, Saint Louis Hospital, 1 Avenue Claude Vellefaux, 75010 Paris, France.

The causes of atherosclerosis are multiple.[1,2] Among the numerous risk factors, 2 are particularly important: hypertension and primary or secondary abnormalities of plasma lipids and lipoproteins.

The incidence of coronary events is positively correlated with the degree of blood pressure elevation, high levels of total cholesterol, low-density lipoprotein (LDL) and very low density lipoprotein (VLDL) cholesterol, triglycerides or VLDL triglycerides, and apoprotein B and low levels of high-density lipoprotein (HDL) cholesterol, apoprotein A_1 and HDL_2.[3,4]

The Lipid Research Clinics Coronary Primary Prevention Trial[5] clearly demonstrates that for every 1% decrease in plasma total cholesterol levels there is a 2% decrease in the frequency of coronary artery disease (CAD). There is also increasing evidence from epidemiologic and intervention studies that triglycerides are an independent major risk factor for CAD. This is supported by angiographic and case-controlled studies as well as by biochemical investigations.[6]

Several important randomized controlled studies have demonstrated that, despite a marked decrease in cerebrovascular events, renal failure and hypertensive cardiomyopathy, antihypertensive treatment has little influence on CAD.[7–9] In contrast to a 32 to 100% decrease in fatal or nonfatal cerebrovascular accidents, CAD complications showed only a moderate mean reduction of 11% after antihypertensive treatment.[10]

The explanation is unclear. It has been suggested that some antihypertensive agents have a deleterious effect by altering lipoproteins, and this may override the benefit of blood pressure reduction. Diuretics and β blockers are the 2 principal pharmacologic agents that are known to alter lipids.

With thiazide diuretics (hydrochlorothiazide, polythiazide, cyclopenthiazide, clopamide, bendroflumethiazide and mefruside), the mean increase in serum triglyceride concentration was 20%, but the mean change in total cholesterol was small (+5 to +8%) because of an increase in VLDL and LDL cholesterol (+22 and +8%, respectively) and a reduction in HDL cholesterol (−20%). Chlorthalidone is also known to have adverse effects on lipid metabolism. With β blockers, the most constant and most obvious disturbances are an increase in total triglycerides (+38%) or VLDL triglycerides and a decrease in HDL cholesterol (−20%). The most pronounced alteration in serum lipids occurred with nonselective β blockers without intrinsic sympathomimetic ac-

TABLE I Summary of Open Safety Studies of Indapamide (2.5 mg/day) on Lipid Parameters

Reference	No. of Pts.	Duration of Treatment	Lipid Fraction Measured
No Lipid or Lipoprotein Effects			
23	442	1–18 mo	Tc-Tg
24	644	3 mo	Tc-Tg
25	41	4–9 mo	Tc-Tg
26	27	2 mo	Tc-Tg-LDLc-VLDLc
27	79	48 wks	Tc-HDLc
28	14	8 wks	Tc-Tg-LDLc-HDLc VLDLc
29	22	3 mo	Tc-Tg-LDLc-HLDc VLDLc-Apo A_1-B
30	15	2 yrs	Tc-Tg-LDLc-HDLc VLDLc
31	15	6 wks	Tc-HDLc
32	13	24 wks	Tc-Tg-LDLc-HDLc-VLDLc ApoA_1-B
33	52	12 wks	Tc-Tg
34	173	1 yr	Tc-Tg-HDLc
Beneficial and Significant Change in Lipids and Lipoproteins ($p < 0.05$)			
2	20	6 mo	HDLc + 15%
35	11	3 mo	Tc + 16% HDLc + 17% Apo A_1 + 13% Apo A_2 + 17%

Apo = apoprotein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; Tc = total cholesterol; Tg = triglycerides; VLDL = very low density lipoprotein.

TABLE II Summary of Single-Blind (sb) and Double-Blind (db) Placebo Comparisons with Indapamide on Lipid Parameters

Reference	Study Design (Duration of Treatment)	No. of Pts.	Daily Dose (mg)	Lipid Fraction Measured
No Lipid or Lipoprotein Effect				
36	db (8 weeks)	20	2.5	Tc-Tg
37	sb (24 weeks)	17	2.5	Tc-Tg
38	sb (1 year)	105	1 to 3	Tc-HDLc
17	db (24 weeks)	260	2.5	Tc-Tg
39	sb (6–8 weeks)	69	2.5	Tc-Tg-LDLc-HDLc-Tg-VLDL Tg-HDL/ ApoA_1-A_2
Beneficial Change on Lipid Parameters ($p < 0.05$)				
40	sb (16 weeks)	40	2.5	Tg-28% HDL-c + 27%

Abbreviations as in Table I.

tivity.[11–13] Therefore, it is important that blood pressure reduction should not be accompanied by an alteration in blood lipids.[14–16]

Indapamide is an orally active sulfonamide diuretic agent that is useful in the management of mild to moderate essential hypertension, in both young and old patients, decreasing resting systolic and diastolic blood pressures by 10 to 20%.[17]

Blood pressure is reduced by volume contraction and a direct reduction of vascular reactivity.[18,19] Most reports indicate that indapamide has no adverse effects on lipid levels.[3,9] Indapamide thus appears to be unique among diuretics because of its lack of adverse lipid effects.[20–22]

The purpose of this report is to summarize the effect of indapamide, 2.5 mg once daily, on blood lipid parameters by comparison with other antihypertensive drugs.

INDAPAMIDE AND LIPID METABOLISM

Twenty-six studies have been reported, 25 of which have clearly demonstrated that treatment with indapamide is not associated with any significant adverse changes in blood lipid parameters.

Two of the open studies (Table I) conducted by Meyer-Sabellek et al[2] and Yoshino et al[35] detected an increase in total cholesterol due to a significant increase in HDL cholesterol (15 and 17%, respectively; $p < 0.05$), without modification of LDL cholesterol levels. In the study by Yoshino et al,[35] indapamide replaced previous treatment with a thiazide. This resulted in an elevation of total cholesterol and HDL cholesterol levels, and an increase in apoprotein A_1, A_2 lipoprotein fractions. One explanation is that HDL cholesterol and apoprotein A_1 levels had been suppressed by thiazide treatment and that indapamide normalized these 2 parameters.

Five single- and double-blind placebo studies have demonstrated that indapamide therapy has no effect on lipids (Table II). The most important is the study of Beling et al,[17] in which 360 patients were treated with indapamide for 24 weeks. At the end of the study there were no significant changes in total cholesterol and triglyceride levels. In the study by Gerber et al,[39] all lipids and lipoproteins were examined and no disturbances were detected. Cardona et al[40] found treatment with indapamide to decrease the triglyceride concentration significantly (−28%, $p < 0.05$) and to increase HDL cholesterol (+27%, $p < 0.05$).

In 6 studies, indapamide was compared with other antihypertensive drugs, a thiazide diuretic in 5 studies, and a β blocker in the remaining study (Table III).

Weidmann et al[42] compared the effects of indapamide, 2.5 mg/day, or tienilic acid, 250 mg/day, on serum lipid and lipoprotein concentrations in healthy and hypertensive men. After 6 weeks of treatment with tienilic acid, triglycerides and LDL cholesterol increased (+12 and +17%, respectively, $p < 0.05$), whereas indapamide had no effect on these parameters. Neither agent significantly altered HDL cholesterol, total serum cholesterol or apoprotein B concentrations.

In a 2-year study, Yoshino et al[46] compared indapamide with thiazide therapy. There was a significant increase in HDL cholesterol levels (+12%, $p < 0.05$) and in apoprotein A_1 (+24%, $p < 0.05$), apoprotein C_1 (+45%, $p < 0.001$) and apoprotein E (+19%, $p < 0.05$) after 1 year of indapamide treatment. LDL cholesterol levels did not show any significant change during the 2-year study period.

In a multicenter trial, Morledge[45] detected an increase of 9% ($p < 0.05$) and 19% ($p < 0.001$) in total

TABLE III Summary of Comparative Studies Between Indapamide (IDP) and Other Antihypertensive Drugs on Lipid Parameters

Reference	Study Design (Duration of Treatment)	Treatment of Pts. (n)	Daily Dose (mg)	Lipid Fraction Measured
		No Lipid or Lipoprotein Effects with IDP		
41	open (3 years)	IDP (24) HCTZ + amiloride (52)	2.5 50 + 5	Tc
42	sb (6 weeks)	IDP (18) tienilic acid (16)	2.5 250	Tc-HDLc Tc + 12% − LDLc + 17% ($p < 0.05$) Tg-VLDL + 10% ($p < 0.05$)
43	open (1 month)	IDP (12) HCTZ (12)	2.5	Tc-Tg-LDLc
44	open (12 weeks)	IDP (12) nadolol (8)	2.5 160	Tc
		Significant Increased Total Cholesterol with IDP ($p < 0.05$)		
45	db (40 weeks)	IDP (8) IDP (9) HCTZ	2.5 5 50	Tc + 9% Tc + 19% Tc + 10%
		Beneficial and Significant Change on Lipid and Lipoproteins ($p < 0.05$)		
46	open (2 years)	IDP (15) TCMTZ (15)	2.5 2	TC + 14% − HDLc + 12% $ApoA_1$ + 24% $ApoC_{11}$ + 45% ApoE + 19%

db = double-blind; HCTZ = hydrochlorothiazide; sb = single-blind; TCMTZ = trichloromethiazide; other abbreviations as in Table I.

cholesterol levels in patients treated with indapamide, 2.5 and 5 mg/day, respectively.

The increase in serum cholesterol concentration was higher after indapamide, 5 mg/day, than after hydrochorothiazide, 50 mg/day. Further studies are needed to compare indapamide with a standard thiazide agent used in conventional and low-dose therapy.[8,9]

Chemical structure is not thought to be a factor in the lack of lipid effect of indapamide, because another agent of this class of nonthiazide diuretics, clopamide, is known to increase LDL cholesterol concentrations.[47] The vasodilating action of indapamide or the low recommended daily dosage (2.5 mg/day) are possible explanations.

CONCLUSION

Indapamide, 2.5 mg once daily, is effective and safe for the control of mild to moderate hypertension. This new diuretic antihypertensive agent differs from established agents both in chemical structure and in its vascular effects. Indapamide appears to be unique among diuretics because it lacks lipid effects. It may be an optimal diuretic for use in normolipidemic or hyperlipidemic patients becauses it increases HDL but not LDL cholesterol.

REFERENCES

1. Medical Research Council Working Party on Mild Hypertension. *Br Heart J 1988;59:364–378.*

2. Meyer-Sabellek W, Gotzen R, Heitz J, Arntz HR, Schulte KL. Serum lipoprotein levels during long-term treatment of hypertension with indapamide. *Hypertension 1985;7:suppl II:170–174.*

3. Assmann G, Schulte H. The prospective cardiovascular Münster (PROCAM) study: prevalence of hyperlipidemia in persons with hypertension and for diabetes mellitus and the relationship to coronary heart disease. *Am Heart J 1988; 116:1713–1724.*

4. Roberts WC. Factors linking cholesterol to atherosclerotic plaques. *Am J Cardiol 1988;1:495–498.*

5. Lipid Research Clinics—Coronary Primary Prevention Trial Results. 1. Reduction in incidence of coronary heart disease. *JAMA 1984;251:351–364.*

6. Castelli WP. The triglyceride issue: a view from Framingham. *Am Heart J 1986;112:432–437.*

7. Amery A, Lidnen P. Alterations in lipid metabolism induced by antihypertensive therapy. *Drugs 1988;36:suppl 2:1–5.*

8. Ames RP. The effects of antihypertensive drugs on serum lipids and lipoproteins. *Drugs 1986;32:260–278.*

9. Ames RP. The influence of non beta-blocking drugs on the lipid profile: are diuretics outclassed as initial therapy for hypertension? *Am Heart J 1987; 114:998–1006.*

10. Dzau VJ. Mechanism of the interaction of hypertension and hypercholesterolemia in atherogenesis: the effects of antihypertensive agents. *Am Heart J 1988;116:1725–1728.*

11. Gamble CL, Ken DC. Antihypertensive drug therapy in patients with hyperlipidemia and endocrine disorders. *Pract Cardiol 1987;13:93–106.*

12. Krone W, Nagele H. Effects of antihypertensive agents on plasma lipids and lipoprotein metabolism. *Am Heart J 1988;116:1729–1734.*

13. Lardinois LK, Neuman S. The effects of antihypertensive agents on serum lipids and lipoproteins. *Arch Intern Med 1988;148:1280–1288.*

14. Middeke M, Holzgreve H. Review of major intervention studies in hypertension and hyperlipidemia: focus on coronary heart disease. *Am Heart J 1988; 116:1708–1712.*

15. Nakamura H. Effects of antihypertensive drugs on plasma lipids. *Am J Cardiol 1987;60:24E–28E.*

16. Roberts WC. Blood lipid levels and antihypertensive therapy. *Am J Cardiol 1987;60:33E–35E.*

17. Beling S, Vukovich RA, Neiss ES, et al. Long term experience with indapamide. *Am Heart J 1983;106:258–262.*

18. Finch L, Hicks PE, Moore RA. The effects of indapamide on vascular reactivity in experimental hypertension. *Curr Med Res Opin 1977;5:suppl I:44–54.*

19. Uhlich E, Troger C, Knoll W. Effects of indapamide in hypertensive patients and on experimental reactivity. *Curr Med Res Opin 1977;5:suppl I:71–78.*

20. Weidmann P, Ferrier C, Saxenhofer H. Serum lipoproteins during treatment with antihypertensive drugs. *Drugs 1988;35:suppl 6:118–134.*

21. Weinberger MH. Antihypertensive therapy and lipids. *Am J Med 1986;80:*

suppl 2A:64–70.
22. Weinberger MH. Diuretics and their side effects. Dilemma in the treatment of hypertension. *Hypertension 1988;11:suppl II:16–20.*
23. Royer R. Progrès dans le traitement de l'hypertension artérielle: approche clinique issue d'une étude multicentrique française. A propos de 442 cas. *Sem Hop Paris Therap 1976;52:365–368.*
24. Passeron J, Pauly N, Desprat J. Etude multicentrique internationale de l'indapamide dans le traitement de l'hypertension artérielle essentielle. *Vie Méd 1980;(hors série):67–70.*
25. Roux P, Courtois H. Evolution de l'équilibre glycémique au cours du traitement par l'indapamide chez les diabétiques hypertendus. *Vie Méd 1980;(hors série):29–31.*
26. Colo Di G, Cevaro G, Lombardo F, Moratti P, Cicuttini L, Rotolo V. L'Indapamide nel trettamento dell'ipertensione arteriosa essentialle dell'anziona: influenza sui metabolismo glico-lipidico. *Boll Soc Ital Cardiol 1981;26:1527–1530.*
27. Baba S, Amono M, Inura M, Ijuno T, Ishida M. Study on safety of long-term administration of indapamide in patients with essential hypertension. *Geriatr Med 1982;20:1207–1216.*
28. Ferrara LA, Giumetti D, Fasano ML. Once a day Indapamide therapy in hypertension. Effect on the heart and peripheral arterial circulation. *Jpn Heart J 1983;24:731–737.*
29. Gumbrielle T, Darby S, Collins P, Johnson A. Hypokalaemic effect of indapamide treatment of hypertension. *Eur Heart J 1984;5(abstract, suppl I):103.*
30. Scalabrino A, Galeone F, Guintoli R, Guidi G, Birindelli A, Natali A, Saba P. Clinical investigation on long-term effects of indapamide in patients with essential hypertension. *Curr Therap Res 1984;35:17–22.*
31. Gupta YK, Maulik SK, Karmakar HG, Feddy KS. Effects of chronic indapamide and verapamil monotherapy on serum lipids in hypertensive patients. *Acta Pharmacol Toxicol 1986;59:165.*
32. Osei K, Holland G, Falko JM. Indapamide, effects on apoprotein, lipoprotein, and glucoregulation in ambulatory diabetic patients. *Arch Intern Med 1986;146:1973–1977.*
33. Safavian A, Fruitel D. Intérêt du Fludex dans le traitement des hypertensions artérielles résistantes. *Concilia Medica 1986;1:13–32.*
34. Leonetti G, Rappelli A, Salvelti A, Scapellato L. Tolerability and well-being with indapamide in the treatment of mild-moderate hypertension. *Am J Med 1988;84:suppl IB:59–64.*
35. Yoshino G, Kasama T, Iwatani I, Iwai N, Kazuni T, Baba S. Comparison of the effects of indapamide and trichlormethiazide on lipoprotein and apolipoprotein. *Curr Ther Res 1986;39:1027–1031.*
36. Cardona R, Santodomingo E. Pharmacologie clinique de l'indapamide dans l-hypertension artérielle essentielle. *Vie Méd 1980;(hors série):41–43.*
37. Horgan JH, O'Donovan A, Teo KK. Echocardiographic evaluation of left ventricular function in patients showing antihypertensive and biochemical response to indapamide. *Postgrad Med J 1981;57:suppl 2:64–67.*
38. Goto Y, Tanabe A, Tagawa R, Ueshima J, Okajima S, Maeda S, Yokoyama T, Oshikoji T, Higuchi Y, Yamazaki A, Namba T, Tamaka Y, Imokawa H, Yamamoto N, Ijyu S, Usui T, Shimizu A, Hagiwara T. Study on efficacy and safety of long term administration of indapamide in patients with essential hypertension. *Geriatr Med 1982;20:1–19.*
39. Gerber A, Weidmann P, Bianchetti MG, Ferrier C, Laederach K, Mordasini R, Riesen W, Bachmann C. Serum lipoproteins during treatment with the antihypertensive agent indapamide. *Hypertension 1985;7:suppl II:166–169.*
40. Cardona R, Lopez B, Fragachan F. Effects of indapamide on the lipid profile of patients with essential hypertension. Proceedings of the XIVth International Symposium on Indapamide. *Vienna, Nov. 23 1985.*
41. Demanet JC, Degante JP, Hubert C. Safety and therapeutic efficacy in a long term study of indapamide in the treatment of essential hypertension. *Curr Med Res Opin 1977;5:suppl 1:129–136.*
42. Weidmann P, Meier A, Mordasini R, Reisen W, Bachmann C. Diuretic treatment and serum lipoproteins: effects of Pehein E., tienilic acid and Indapamide. *Klin Wochenschr 1981;59:343–346.*
43. Wall-Manning HJ, Doesborg RMN. Randomized cross over trial of indapamide and conventional diuretics in hypertension. Metabolic and renal effects. *NZ Med J 1982;95:19–24.*
44. Houde M, Carriere S. Indapamide dans le traitment ambulatoire de l'hypertension artérielle: modifications des catécholamines sériques. *Curr Med Res Opin 1983;8:suppl 3:214–223.*
45. Morledge JH. Clinical efficacy and safety of indapamide in essential hypertension. *Am Heart J 1983;106:229–232.*
46. Yoshino G, Iwai M, Kazum T, Matsuba K, Iwatami I, Kasama T. Comparison of the long-term effects of indapamide and trichlormethiazide on lipoprotein and apolipoprotein. *Curr Therap Res 1987;42:607–613.*
47. Perry HM. Some wrong-way chemical changes during antihypertensive treatment: comparison of indapamide and related agents. *Am Heart J 1983;106:251–257.*

The American Journal of Cardiology

19.4.91

MAY 22, 1990

A Symposium: The Renin-Angiotensin System — Tissue Specific Issues

CALCUTTA UNIVERSITY CENTRAL LIBRARY

GUEST EDITOR:
William W. Parmley, MD
Professor of Medicine
Chief of Cardiology
University of California San Francisco
Moffitt/Long Hospitals
San Francisco, California

A YORKE MEDICAL JOURNAL/CAHNERS PUBLISHING COMPANY

Publisher's Note

The opinions expressed in this presentation are those of the panelists and are not attributable to the sponsor or the publisher, editor, or editorial board of The American Journal of Cardiology. Clinical judgment must guide each physician in weighing the benefits of treatment against the risk of toxicity. References made in the articles may indicate uses of drugs at dosages, for periods of time, and in combinations not included in the current prescribing information.

Editor's suggestion: The symposium issues for a full year should be bound together separately from the regular issues.

The American Journal of Cardiology

MAY 22, 1990 VOL. 65 NO. 19

A Symposium: The Renin-Angiotensin System — Tissue Specific Issues

GUEST EDITOR:

William W. Parmley, MD
Professor of Medicine
Chief of Cardiology
University of California San Francisco
Moffitt/Long Hospitals
San Francisco, California

This symposium was held March 18, 1989, in Anaheim, California, and was supported by an educational grant from Merck Sharp & Dohme.

EDITOR-IN-CHIEF
William C. Roberts, MD

PRODUCTION EDITOR
Joan Gunning

MANAGING EDITOR, SPECIAL PROJECTS
Judith Wagner

PUBLISHER, SPECIAL PROJECTS
Kenton T. Finch

PROOF EDITOR
Mary Crowell

THE AMERICAN JOURNAL OF CARDIOLOGY.® (ISSN 0002-9149) May 22, 1990, Vol. 65, No. 19 (USPS: 505–750).

Member, American Business Press, Inc. and Audit Bureau of Circulations. Published 4 times in January, February, March, May, June, July, September and October, 3 times in April, August and November, and 2 times in December, by The Cahners Publishing Company, a Division of Reed Publishing USA, 275 Washington St., Newton, MA 02158-1630. Terrence M. McDermott, President; Jerry D. Neth, Vice President/Publishing Operations; J.J. Walsh, Financial Vice President/Magazine Division; Thomas J. Dellamaria, Vice President/Production and Manufacturing.

SUBSCRIPTIONS: Solicited only from cardiologists and other physicians. Publisher reserves the right to refuse unqualified subscribers. Subscribers agree that no article or any part thereof published in any editions of the American Journal of Cardiology received under this subscription agreement may be copied, recorded or reproduced in any form or by any means, electronic or mechanical, including, among other things, photocopying or the storing of part or all of such articles on any information retrieval system, without the written permission of the Publisher. Address correspondence regarding subscriptions and changes of address to: THE AMERICAN JOURNAL OF CARDIOLOGY, 44 Cook Street, Denver, Colorado 80206-5800 (1-800-637-6073). Please include your zip code and, in case of change of address, copy of old address label. Changes of address must reach the Journal one month preceding month of issue. Single copy price: Regular issues $10.00; Symposium and special issues $12.00. Subscription rate for individuals in field of publication: United States 1 year $66, 2 years $112, 3 years $158; Canada and all other countries 1 year $105, 2 years $178, 3 years $252; Residents and Medical Students: United States 1 year $33; Canada & all other countries 1 year $85. Institutions: United States 1 year $95, 2 years $162, 3 years $228; Canada & all other countries 1 year $125, 2 years $213, 3 years $300. Air Mail available at additional charge of $150 per year. The Journal is not responsible for replacing missing issues unless the Circulation Department is notified of nonreceipt within 3 months of issue date.

Second class postage paid at Denver, CO, and at additional mailing office. Printed in U.S.A. Trademark™ in U.S. Patent Office. © Copyright 1990 by Reed Publishing USA: Saul Goldweitz, Chairman; Ronald G. Segel, President and Chief Executive Officer. All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording or by any information storage retrieval system, without permission of the copyright owner. Prices on bulk reprints of articles available on request.

The Publisher assumes no liability for any material published in the Journal. All statements are the responsibility of the authors.

MANUSCRIPTS: Address all manuscripts to William C. Roberts, MD. Editor-in-Chief, the American Journal of Cardiology; 7960 Old Georgetown Road, Suite 2C, Bethesda, Maryland 20814.

POSTMASTER: Send address changes to: The American Journal of Cardiology, 44 Cook Street, Denver, Colorado 80206-5800.

Cahners Publishing Company, A Division of Reed Publishing USA □ Specialized Business Magazines for Building & Construction □ Manufacturing □ Foodservice & Lodging □ Electronics & Computers □ Interior Design □ Printing □ Publishing □ Industrial Research & Technology □ Health Care □ Entertainment.



CONTENTS

The American Journal of Cardiology

MAY 22, 1990 VOL. 65 NO. 19

A SYMPOSIUM: THE RENIN-ANGIOTENSIN SYSTEM — TISSUE SPECIFIC ISSUES

1 I **The Angiotensin-Converting Enzyme Inhibitor: A Drug for All Seasons** William W. Parmley

3 I **Tissue Renin-Angiotensin Systems in the Heart and Vasculature: Possible Involvement in the Cardiovascular Actions of Converting Enzyme Inhibitors** Thomas Unger and Peter Gohlke

11 I **Issues Surrounding a Local Cardiac Renin System and the Beneficial Actions of Angiotensin-Converting Enzyme Inhibitors in Ischemic Myocardium** Charles S. Sweet

14 I **Myocardial Ischemia, Reperfusion and Free Radical Injury** Benedict R. Lucchesi

24 I **Captopril and Enalaprilat Do Not Scavenge the Superoxide Anion** Rakesh C. Kukreja, Hermes A. Kontos, and Michael L. Hess

28 I **Neuroendocrine Activation After Acute Myocardial Infarction** Jay N. Cohn

32 I **Neuroendocrine Activation in Acute Myocardial Infarction** T. Barry Levine

35 I **Protection of the Myocardium During Myocardial Infarction: Pharmacologic Protection During Thrombolytic Therapy** James T. Willerson and L. Maximilian Buja

42 I **Arrhythmias and Mortality in Congestive Heart Failure** John Kjekshus

49 I **Renal Protective Effects of Angiotensin-Converting Enzyme Inhibition** William F. Keane and Bruce E. Shapiro

The American Journal of Cardiology

The Angiotensin-Converting Enzyme Inhibitor: A Drug for All Seasons

William W. Parmley, MD

Since the introduction of angiotensin-converting enzyme (ACE) inhibitors, their use has increased dramatically. Initially approved for the treatment of hypertension, it became evident that they were of considerable value as afterload-reducing agents in patients with congestive heart failure. As one of the class of vasodilator drugs, ACE inhibitors have shown the ability to prolong life in patients with severe congestive heart failure. These beneficial effects have led to a broadened search for other applications of these drugs. This search has been spurred, in part, by the discovery that the renin-angiotensin system is located in a wide variety of body tissues. Thus, the potential for a variety of physiologic benefits is heightened by the widespread presence of this important system. This symposium highlights some of the ramifications of the presence of the renin-angiotensin system in a variety of body tissues.

Unger and Gohlke review the local renin-angiotensin systems in the heart and vascular walls, and the evidence that these systems may play an important role in hypertension and ventricular hypertrophy. They also discuss the relationship of the renin-angiotensin system to other hormonal mediators such as the kinins. Of considerable importance are the potential effects of converting enzyme inhibitors on reversing cardiac hypertrophy and altering the peripheral vasculature. This review summarizes the experimental evidence that ACE inhibitors are important not only because of their effects on the plasma renin angiotensin system, but also because local tissue inhibition may play an important role in the actions of these drugs. Sweet extends these findings to the potential effects of ACE inhibitors in the heart, particularly in ischemic myocardium. Sweet discusses the role of bradykinin and prostacyclin, and the potential for sulfhydryl-containing ACE inhibitors to be scavengers of oxygen free radicals.

These issues are further discussed by Lucchesi who analyzes the potential benefit of ACE inhibitors on reperfusion injury after ischemia. Lucchesi focuses on the role of the neutrophil and its contribution to tissue injury, and reviews the various interventions that have been proposed to reduce reperfusion injury, particularly free radical scavengers. Lucchesi discusses the fact that studies have shown both positive and negative effects with free radical scavengers such as superoxide dismutase, and that many of these differing results may be related to individual animal models or the short half-life of the protective substances, or both. Kukreja et al provide the counterpoint argument to the potential for ACE inhibitors to protect against injury after ischemia and reperfusion. In their study, captopril and enalaprilat did not show significant inhibition of the free radical mechanisms but may have acted as a nonspecific antioxidant.

Besides providing protection from reperfusion injury after ischemia, there is theoretical benefit if ACE inhibitors are given during and after an acute myocardial infarction. Cohn and Levine describe the neurohormonal responses that occur in acute myocardial infarction. This complex response involves the activation of the sympathetic nervous system, the antidiuretic hormone system, and the release of atrial natriuretic peptide. The potential for this complex interaction can be to provide either beneficial or deleterious effects. Cohn reviews the Veterans Administration Cooperative Study that evaluated the infusion of sodium nitroprusside for 48 hours in patients after acute myocardial infarction. This study was designed to test the hypothesis that vasoconstriction might be an adverse effect during this early period after acute infarction. Nitroprusside appeared to be more favorable when given later and in the presence of predominantly



From the University of California, San Francisco, San Francisco, California.

Address for reprints: William W. Parmley, MD, University of California, San Francisco, Cardiology Division, 502 Parnassus, Room 1186, San Francisco, California 94143.

systolic dysfunction. This study emphasizes the complex interplay between neurohormonal mechanisms and the challenge of intervening in a way that will produce benefit.

Willerson and Buja review a variety of agents that have been evaluated relative to their protection during thrombolytic therapy. These include: thromboxane receptor antagonist and synthesis inhibitors, serotonin and receptor antagonists, leukotriene synthesis inhibitors or receptor antagonists, and aspirin. In addition, he reviews the potential benefit of calcium antagonists, β blockers, phospholipase antagonists and free radical scavengers. The complex and changing biology of acute myocardial infarction during thrombolysis raises the real possibility that combined therapy with selected agents may be of greater benefit than therapy with individual agents alone.

One of the major unsolved issues related to the treatment of congestive heart failure is the high incidence of serious ventricular arrhythmias and sudden death which may range from 20 to 50% in patients with heart failure. Although ACE inhibitors have been shown to reduce premature ventricular contractions, unfortunately they have not yet demonstrated an ability to reduce the incidence of sudden death. No other drugs have shown this benefit in the presence of congestive heart failure, although in the postmyocardial infarction setting, the β blockers have reduced the incidence of serious arrhythmias and sudden death. The fact that high circulating neurohormonal levels are predictive of an adverse outcome suggests the potential for drugs that interfere with the neurohormonal systems to produce benefit. Keane and Shapiro examine the potential renal protective effects of ACE inhibitors. Although the predominant beneficial effect of this therapy may be mediated by hemodynamic changes, there is additional evidence that there may also be some effect on growth/proliferation of glomerular cells.

As one reviews the contributions to this symposium, it is clear that the ACE inhibitors are likely to have a wide variety of effects, in part because of the ubiquitous nature of the tissue renin-angiotensin system. It is clear that future studies may help us to unravel the potential beneficial effects of these agents in a wide variety of circumstances and thus greatly enhance our knowledge of the beneficial and detrimental effects of renin-angiotensin stimulation and blockade.

Tissue Renin-Angiotensin Systems in the Heart and Vasculature: Possible Involvement in the Cardiovascular Actions of Converting Enzyme Inhibitors

Thomas Unger, MD, and Peter Gohlke, PhD

The existence of independently functioning local renin-angiotensin systems in a number of tissues has been firmly established by biochemical and functional evidence and, most recently, by the demonstration of genetic messages for components of the renin-angiotensin systems, such as renin and angiotensinogen, in several organs. In this review, local renin-angiotensin systems in the heart and vascular walls are described and the contribution of a local inhibition of converting enzymes to the cardiovascular actions of converting enzyme inhibitors is discussed. Most of the studies cited support the hypothesis that an inhibition of cardiac converting enzyme may be involved in the beneficial hemodynamic and metabolic actions of converting enzyme inhibitors in cardiovascular disease, such as hypertension and congestive heart failure, independent of the circulating renin-angiotensin system. Local effects on cardiac converting enzyme may contribute to the ability of converting enzyme inhibitors to reduce cardiac hypertrophy. Similarly, local converting enzyme inhibition in the vascular wall may not only constitute a mechanism involved in the antihypertensive effects of converting enzyme inhibitors, but may also contribute to the regression of hypertension-induced vascular hypertrophy. In addition to reduced local angiotensin II generation, converting enzyme inhibition may engender a potentiation of the local effects of kinins. This mechanism may be more important to the cardiovascular actions of converting enzyme inhibitors than initially thought.

(Am J Cardiol 1990;65:3 I–10 I)

From the Department of Pharmacology and German Institute for High Blood Pressure Research, University of Heidelberg, Federal Republic of Germany.

Address for reprints: Thomas Unger, MD, Department of Pharmacology, University of Heidelberg, Im Neuenheimer Feld 366, D-6900 Heidelberg, Federal Republic of Germany.

Most of the early clinical pharmacologic studies on converting enzyme inhibitors (CEIs) dealt with acute effects of the drugs on blood pressure and parameters of the renin-angiotensin system. It has been consistently demonstrated that on CE administration, expected changes of blood parameters of the renin-angiotensin system occurred; i.e., angiotensin II (A-II) decreased, angiotensin I (A-I) increased, CE activity was inhibited, renin activity increased due to the withdrawal of negative feedback inhibition by A-II, and aldosterone levels of plasma or urine were decreased. However, in clinical cases of long-term treatment with CEIs, it was revealed that this simple scheme had to be reconsidered. It is hypothesized that local angiotensin synthesis in cardiovascular organs, i.e., the vasculature, heart, adrenal glands and the brain, may be important. The following review focuses on the evidence for (1) local renin-angiotensin systems in the heart and the vascular walls; and (2) the possible contribution of local CE inhibition in the heart and vascular walls to the systemic cardiovascular actions of CEIs.

EVIDENCE FOR A LOCAL RENIN-ANGIOTENSIN SYSTEM IN THE HEART

Evidence for a local renin-angiotensin system in the heart has been obtained by the isolation and biochemical characterization of the various components of the system from heart tissue and more recently by the demonstration of renin and angiotensinogen messenger ribonucleic acid in the cardiac tissues of rats and mice.[1–3]

The myocardial levels of angiotensin peptides were measured in rhesus monkeys (Fig. 1). A-II was higher in the atria than in the ventricles and higher in the right than in the left atrium.[4] Perfusion of isolated rat hearts with renin led to a concentration-dependent release of A-I and A-II and perfusion with A-I to a release of A-II. The A-II release was prevented by the addition of CEI to the perfusate.[3] The conversion of A-I to A-II in untreated hearts was 7%, which corresponded to a production of A-II at a rate of 0.8 pmol/min.[5]

Inhibition of cardiac A-II generation by CEIs has also been demonstrated in ex vivo experiments. Isolated hearts from rats pretreated with CEI reduced A-II levels in the effluent when perfused with A-I.[6] Direct measurement of CE activity in heart tissue lends further support to a local cardiac A-II generation system in the heart. Acute and chronic oral antihypertensive treatment of spontaneously hypertensive rats (SHRs) with the CEIs enalapril, rami-

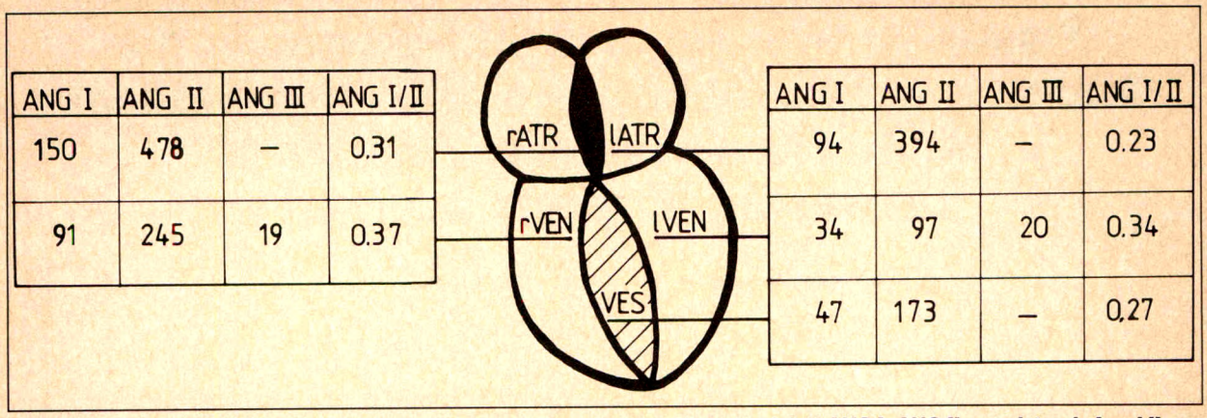


FIGURE 1. Angiotensin concentrations in cardiac tissue of monkey (fmol/g wet weight). ANG I, ANG II = angiotensin I and II, respectively.

pril or perindopril inhibited the CE activity in cardiac tissue; this effect was demonstrable as early as 15 minutes after oral administration of CEI.[7–9]

CARDIAC EFFECTS OF ANGIOTENSIN II

A-II exerts pronounced effects on the heart. In addition to its marked vasoconstrictor effect on coronary arteries,[10] exogenously administered A-II is known to be an effective inotropic agent enhancing myocardial contractility by both direct and indirect myotropic mechanisms. With the use of isolated preparations, A-II has been found, with rare exceptions,[11] to exert a positive inotropic influence on myocardial function. A major focus of investigative effort in this area has been the separation of direct and indirect positive inotropism of A-II, the latter being primarily due to its effects on sympathetic nervous function. When sympathetic facilitation was carefully avoided or excluded, dose-dependent, direct, positive, inotropic effects of A-II have been shown in isolated atria and papillary muscle strips of rabbits,[11] dogs,[12] cats[13,14] and guinea pigs.[10]

The precise mechanism by which the myotropic effects of A-II are mediated is not known, but the recent identification of myocardial A-II–binding sites[15] suggests modulation of intracellular calcium via the phosphatidyl inositol system after A-II receptor stimulation. In addition, A-II may influence the heart by facilitating cardiac sympathetic nerve action, thus contributing to its inotropic actions.[3]

FUNCTIONAL ASPECTS OF CARDIAC CONVERTING ENZYME INHIBITION

Inhibition of local CE in the heart was investigated in several experimental studies using models of myocardial ischemia and cardiac hypertrophy. Ex vivo and in vitro studies with the CEI captopril revealed that CEIs can protect isolated perfused rat hearts from reperfusion arrhythmia,[16] which was exaggerated by A-I and A-II. CEI treatment abolished the arrhythmogenic effects of A-I, but did not affect those of A-II.[17–19] In addition, hearts pretreated with CEIs released markedly less lactate dehydrogenase, creatinine kinase and lactate, while the myocardial concentrations of glycogen, adenosine triphosphate and creatinine phosphate were elevated. CEIs also improved cardiac function in this model, as evidenced by enhanced left ventricular pressure, contractility and coronary flow.[18–20]

Role of bradykinin: Similar enzymatic and metabolic effects, as with CEIs, were obtained with bradykinin in the perfusate at concentrations too low to have any cardiodynamic action.[19–21] The specificity of bradykinin-induced effects was underlined by the finding that the cardioprotective actions of bradykinin and of CEIs were obliterated by a bradykinin antagonist.[22] Thus, the beneficial actions of CEIs in the heart could be mediated not only by a suppression of local A-II generation, but also by a potentiation of local kinin actions. Bradykinin has been shown to increase coronary and capillary flows and glucose uptake in isolated hearts and cardiac myocytes.[23,24] A bradykinin-induced stimulation of cardiac prostacyclin biosynthesis,[25,26] tissue plasminogen activator,[27] and endothelium-derived relaxing factor release,[28] have to be taken into account as mechanisms by which a bradykinin potentiation might contribute to the cardiac actions of CEIs.

Sympathetic transmission: Inhibition of sympathetic transmission in the heart may be an additional factor in the cardiac actions of CEIs. In isolated hearts, CEIs (captopril, enalapril, ramipril) were shown to reduce noradrenaline overflow in ischemia[17,29] and to antagonize the effects of sympathetic nerve stimulation on coronary flow and contractility (Fig. 2).[30] Inhibitory actions on cardiac sympathetic transmission might be related to reduced local A-II synthesis.[3]

EFFECTS OF CONVERTING ENZYME INHIBITORS ON CARDIAC HYPERTROPHY

CEIs can prevent or reduce hypertension-induced cardiac hypertrophy. Regression of left ventricular hypertrophy by CEIs was demonstrated in normal rats[31] and in different forms of experimental hypertension in rats, such as Dahl salt-sensitive rats[32] and SHRs.[33] A significant decrease in left ventricular mass followed by prolonged (3 to 7 months) treatment with CEIs has been observed in hypertensive patients.[34,35]

When rats with experimentally induced aortic stenosis were treated for several weeks with equiantihypertensive doses of the CEI ramipril, the calcium antagonist

nifedipine and the vasodilator dihydralazine, cardiac hypertrophy developed in the nifedipine- and dihydralazine-treated rats, but not in the ramipril-treated rats. In contrast, the plasma A-II concentrations were only reduced in the group treated with CEIs.[20,36] In a similar study using the same experimental model of hypertension, left ventricular hypertrophy was significantly blunted by the CEI quinapril.[37]

Because of documented cell proliferative effects of A-II, findings suggest that CEIs prevent cardiac hypertrophy, not only through their antihypertensive actions (i.e., by afterload reduction) but also more specifically by reducing systemic or local A-II synthesis. The pathophysiologic role of A-II as a growth factor[38] leading to cardiac and vascular hypertrophy in hypertension needs to be elucidated. Future research should investigate how effectively and specifically the cell proliferative actions of A-II can be antagonized by CEIs.

EFFECTS OF CONVERTING ENZYME INHIBITORS IN CONGESTIVE HEART FAILURE

Clinically, CEIs have been successfully introduced into the treatment of congestive heart failure. The addition of enalapril to conventional drug therapy significantly reduced mortality in advanced stages (New York Heart Association class IV) of this disease.[39] The beneficial effect of CEIs cannot be explained on the basis of afterload reduction alone. It appears that direct cardiac actions play an important role. The therapeutic efficacy of captopril in congestive heart failure has been reviewed by Romankiewicz.[40] More recent reviews are also available.[41–49]

RENIN-ANGIOTENSIN SYSTEM IN THE VASCULAR WALL

The idea that vascular renin may contribute locally to blood pressure regulation and hypertension independent of the renin-angiotensin system[50–53] has gained substantial support in recent years by the biochemical presence of the components of the renin-angiotensin system and of genetic material required for local angiotensin production in the vascular wall.[54–57]

Locally generated vascular angiotensin may be involved in a variety of hemodynamic functions, including direct or sympathetically mediated vasoconstriction and vascular spasm, and may also modulate the vascular angiotensin receptors and their response to circulating angiotensin. In addition, local angiotensin may induce cell proliferation and contribute to inflammatory vascular response as well as edema formation.[56]

CONVERTING ENZYME IN THE VASCULAR WALL: LOCALIZATION OF VASCULAR CONVERTING ENZYME

CE has been found in the vascular tissues of large and small arteries, and in the veins of humans and various animal species, by using methods to measure enzyme activity and, more recently, by immunofluorescence or radioinhibitor binding assays.[58–60] In most of these studies, the enzyme was found predominantly in the endothelial layer, but also occurred in the adventitia.[60,61] Velletri and Bean[62] demonstrated that a substantial portion of enzyme activity was localized within the tunica media of rat aorta, suggesting that A-II may be generated in vascular smooth muscle. Saye et al[63] observed that A-I contracts endothelium-denuded rings of rabbit aorta suggesting a conversion of A-I to A-II in extraendothelial layers of the vascular wall. Other investigators, however, have not been able to detect appreciable amounts of the enzyme in the medial layer of blood vessels.[60,61] Localization studies and the evidence cited for angiotensinogen and renin production in endothelial cells points to the endothelium as the major site of vascular A-II synthesis (Fig. 3).

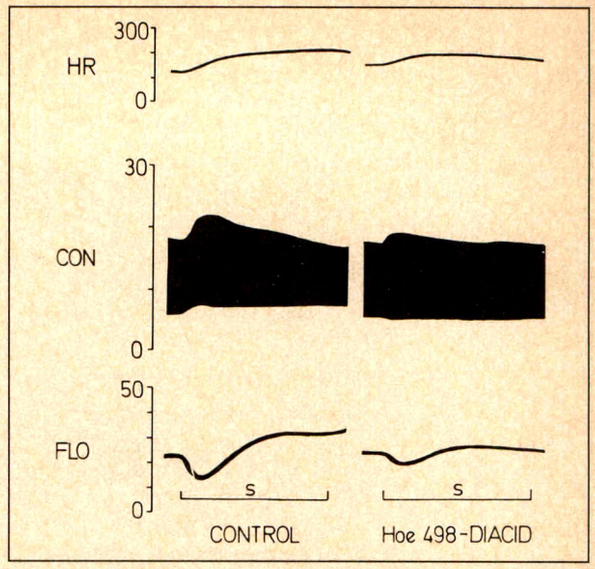


FIGURE 2. Influence of ramiprilat (Hoe 498-diacid) (10 μg/ml/min) on the effects of sympathetic nerve stimulation in isolated rabbit hearts. CON = force of contraction (G); FLO = coronary flow (ml/min); HR = heart rate (beats/min); s = stimulation period. (Reprinted with permission from *Eur J Pharmacol.*[86])

Specificity of vascular converting enzyme: CE can degrade a number of vasoactive peptides in addition to A-I.[64] CE-dependent metabolism of these peptides may have as much of an impact on vascular tone and function as the A-II-generating capacity of the enzyme. In addition, there is growing evidence that CE is not the only enzyme to generate A-II in the vascular wall.[65] Thus, inhibition of vascular CE by CEI may not abolish total A-II-synthesizing capacity in some vascular territories where the homeostasis of the local renin-angiotensin system is maintained to some extent by non-CE A-II-generating enzymes. This may explain why A-II, at reduced concentrations, was still measurable in the aortic wall after single-dose oral CEI treatment with ramipril.[4]

EFFECT OF CONVERTING ENZYME INHIBITORS ON VASCULAR CONVERTING ENZYME ACTIVITY: INHIBITION OF VASCULAR CONVERTING ENZYME

Indirect evidence for vascular CE inhibition, after systemic CEI treatment, was presented in earlier studies reporting on rats with renal hypertension. In these experi-

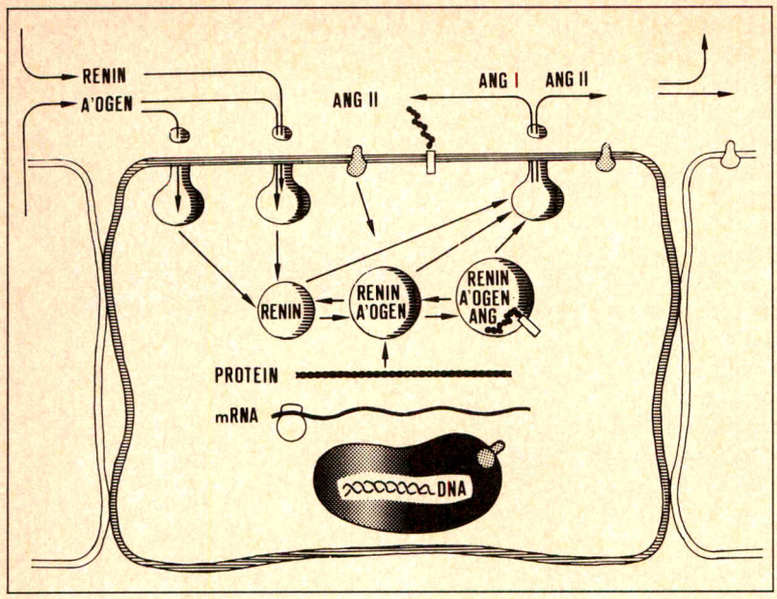


FIGURE 3. Model for local angiotensin II (ANG II) generation in a vascular endothelial cell. Renin and angiotensiongen (A'OGEN) may be taken up from the circulating blood by receptor endocytosis or locally synthesized in the cell. ANG II is synthesized inside the cell but can also be generated outside the cell when intracellularly synthesized angiotensin I (ANG I) is released by exocytosis and gets in contact with converting enzyme at the luminal side of the cell membrane. ANG II can bind to receptors on the same cell (autocrine) or on adjacent cells (paracrine) or on its nuclear receptors. DNA = deoxyribonucleic acid; mRNA = messenger ribonucleic acid.

ments, a slow decrease in vascular renin-like activity, after bilateral nephrectomy, correlated better with a slow decline in blood pressure and depressor responses to blockers of the renin-angiotensin system than did a rapid decrease in plasma renin activity.[57] In further experiments, it was demonstrated that chronic oral antihypertensive treatment of SHRs with the CEI captopril increased renin concentrations in the vascular wall of the aorta.[66,67]

Direct evidence for inhibition of CE in the vascular wall after oral treatment with CEIs has been documented by several research groups. In a series of experiments in SHRs, Cohen and Kurz,[68] and Cohen et al[69] demonstrated that acute oral treatment with captopril and enalapril, at antihypertensive doses, dramatically reduced CE activity in the aorta, mesenteric and carotid arteries, as well as in the vena cava and the mesenteric and jugular veins. In contrast to the CE inhibition in the blood, CE inhibition in the arterial walls persisted for more than 24 hours.

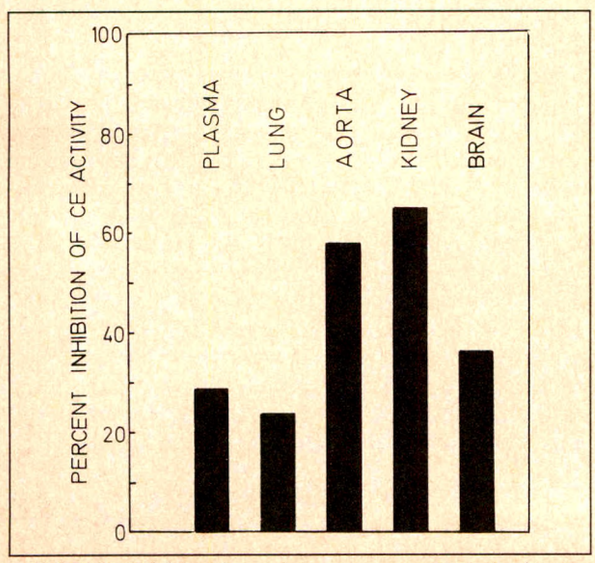


FIGURE 4. Inhibition of converting enzyme activity in plasma and different organs after 4 weeks of oral antihypertensive treatment with enalapril, MK421 (10 mg/kg/day) in stroke-prone spontaneously hypertensive rats.

Prolonged inhibition of CE activity in the aortic wall, but not in the blood serum, after repeated intraperitoneal injections of captopril was also observed by Velletri and Bean.[62] In their laboratory, differences in extent and duration of aortic CE inhibition after acute oral administration of CEI in rats were observed. Antihypertensive doses of ramipril and enalapril, which had similar inhibitory effects on plasma CE activity (1 and 30 mg/kg, respectively), resulted in differential effects. Ramipril produced more than 90% inhibition of the aortic enzyme, which lasted more than 48 hours, whereas enalapril produced a less pronounced CE inhibition of shorter duration.[8] Similar findings were reported by Chevillard et al[70] who compared CE inhibitory actions of trandolapril and enalapril in blood serum and various tissues, including the aorta, after single oral subdepressor doses (3 to 300 μg/kg) of the 2 compounds in normotensive rats. At doses that equally inhibited serum CE activity, trandolapril inhibited aortic CE to a greater extent than enalapril. Twenty-four hours after dosing, aortic CE was still inhibited by approximately 40% in the enalapril group, with a tendency back to control values, whereas aortic CE was still maximally (>90%) inhibited in the trandolapril group. Chronic oral CEI treatment with enalapril, ramipril and perindopril markedly inhibited the enzyme in a number of tissues, including the aortic and mesenteric wall (Fig. 4).[7,8,71] Differences in CEI with respect to vascular CE inhibition were observed in these studies; ramipril was more potent than perindopril and enalapril.

Antihypertensive actions of converting enzyme inhibitors and vascular converting enzyme inhibition: Attempts to relate CE inhibition in the vascular wall, in vivo,

to the antihypertensive effects of CEI, where the effect of these drugs on tissue CE are clearly separated from those in the plasma renin-angiotensin system, have been difficult to design. One experimental approach, elimination of plasma renin-angiotensin system by bilateral nephrectomy, has provided evidence that a stimulated renin-angiotensin system in the vascular wall may contribute to the maintenance of elevated blood pressure and that the vascular renin-angiotensin system is sensitive to specific renin-angiotensin system inhibitor treatment.[57] Other results have shown that oral treatment with CEIs reduced vascular CE activity and vascular A-II concentrations independent of the plasma renin-angiotensin system.[14] A single oral dose of the CEI ramipril (10 mg/kg) was given to rabbits that had undergone bilateral nephrectomy 20 hours before to eliminate circulating renin as a confounding factor. Four hours after treatment, tissue A-II concentrations were found to be significantly reduced in the vascular wall of the aorta compared with vehicle-treated control concentrations.[71]

In a second approach to the question of how tissue CE inhibition relates to antihypertensive effects of CEI, CEI-induced changes in blood pressure were correlated with the degree of the renin-angiotensin system inhibition in plasma vs tissue. Nakata et al[72] treated SHRs and 2-kidney, 1-clip renal hypertensive rats orally with CEI SA 446 for 1 week and found that a maximal decrease in blood pressure correlated with a maximal CE inhibition in the aorta, but not in the brain, lung, heart or in the blood. Nambu et al[73] investigated the tissue distribution of ^{14}C captopril and ^{14}C alacepril, a captopril-related drug, after a single oral dose was administered to renal hypertensive rats. They found that the tissue distribution of both drugs correlated with the local CE inhibition in serum, lung, aorta and kidneys. Although the extent and duration of antihypertensive effects of the inhibitors could not be directly related to CE inhibition in the specific tissues, differences in the pharmacologic profile of the drugs were more strongly associated with the respective total CE inhibition in serum plus tissues than with the individual CE inhibition in serum or tissues.

In a third experimental approach, the drugs were withdrawn after extended periods of treatment. Persistent post-treatment blood pressure reduction was related to post-treatment changes in the plasma renin-angiotensin system or tissue CE. Stroke-prone SHRs were treated orally for several weeks with CEIs enalapril (30 mg/kg/day) and ramipril (3 mg/kg/day). Blood pressure was normalized and plasma and tissue CE in various organs was inhibited during treatment. On withdrawal of the drugs, reduced pressor responses to intravenous A-I and reduced CE activity in the blood plasma were restored to normal within 1 day. Blood pressure remained decreased for an additional 2 weeks and CE inhibition persisted in the kidney and aortic and mesenteric vascular walls.[8,74] These findings demonstrated that the prolonged antihypertensive action of CEI was unrelated to CE inhibition in the plasma and lung endothelium, but was associated with persistent CE inhibition in the kidney and the aortic and mesenteric vascular walls.

In similar experiments, Longman and Howlett[75] studied the relationship between the blood pressure–reducing activity of CEIs and inhibition of plasma and tissue CE in sodium deficient normotensive rats. Tissue CE activity in the aorta, mesenteric bed and lung was inhibited for up to 96 hours after cessation of a 3-week course of treatment, whereas a reduction in blood pressure and inhibition of plasma CE lasted only 48 hours after treatment. Although it appears that blood pressure reduction followed inhibition of the plasma renin-angiotensin system rather than vascular wall CE, it is pointed out that because of sodium depletion before treatment, the plasma renin-angiotensin system was stimulated in these rats, increasing its importance in blood pressure control. Nakamura et al[76] reported a vascular tissue CE inhibition in SHRs after a single oral dose of the CEI cilazapril (0.3 and 3 mg/kg). They observed a persistent 24-hour inhibition of CE in the aortic, carotid, brachial and femoral arteries and veins, and in the pulmonary vein. Inhibition in the mesenteric and renal vessels and in the pulmonary, subclavian and circle of Willis arteries lasted <24 hours after dosing. A decrease in blood pressure was maximal between 4 and 6 hours and was significant 24 hours after treatment. As in previous studies, a marked inhibition of CE in the larger arteries and veins represents a consistent feature of systemic CEI treatment. This raises the possibility that vascular changes induced by CEI drugs may be related not only to vascular resistance controlled by the small arteries, but also to the distensibility of larger vessels.

SIGNIFICANCE OF CONVERTING ENZYME INHIBITION IN LARGE ARTERIES

The large conduit arteries, i.e., the aorta and the coronary, carotid and renal arteries, have long been underestimated with respect to their participation in blood flow regulation. Recent evidence indicates that these vessels, through their conduit and buffering functions, play an important role in blood pressure control and within pathophysiologic events in many cardiovascular disorders. An increasing number of experimental and clinical studies suggest that the therapeutic benefit of CEIs in hypertension and congestive heart failure can be partially explained by their effect on vascular compliance and distensibility of the large arteries. This aspect of vascular CEI action has recently been reviewed by Dzau and Safar.[77] They concluded that increases in arterial caliber and distensibility may contribute to the cardiovascular effects of CEIs, promoting regression of cardiac hypertrophy, reducing hypertensive vascular injury and preventing congestive heart failure.

FUNCTIONAL ASPECTS OF VASCULAR CONVERTING ENZYME INHIBITION

Locally generated A-II may exert different actions to influence vascular tone and distensibility. These include direct vasoconstriction by stimulation of angiotensin receptors on the smooth muscle cells of the vascular media,[78] facilitation of adrenergic transmission leading to vasoconstriction by an increased vascular tone,[79,80] and

TABLE I Cross-Sectional Area of Arterial Media at Different Sites of the Arterial Tree

	10^3 × Cross-Sectional Area (μm^2)							
				Intrarenal Arteries				Peripheral
	Thoracic Aorta	Abdominal Aorta	Renal Artery	1st Divis.	2nd Divis.	3rd Divis.	4th Divis.	Renal Arteries
Treated SHRSP	346 ± 28	298 ± 18	65 ± 17	21 ± 4	14 ± 3	4.4 ± 0.8	1.7 ± 0.3	0.7 ± 0.2
Untreated SHRSP	633 ± 101	433 ± 61	103 ± 20	40 ± 6	26 ± 5	8.3 ± 2.3	4.1 ± 1.2	1.3 ± 0.4
WKY	378 ± 31	335 ± 11	71 ± 13	20 ± 2	12 ± 1	5.2 ± 0.8	1.6 ± 0.1	0.8 ± 0.3

Values are mean ± standard error of the mean.
Divis. = division; SHRSP = stroke-prone spontaneously hypertensive rats; WKY = Wistar Kyoto control rats.
Reproduced with permission from *Clin Sci.*[26]

stimulation of sodium ion and calcium ion transport systems across the cell membrane, as demonstrated in cultured vascular smooth muscle cells.[81] In addition, A-II may exert vasodilatory actions through stimulation of endothelial prostacyclin synthesis,[82] although the functional significance of this effect is still unclear.

Evidence for a pathophysiologic role of the stimulated vascular renin-angiotensin system in hypertension has been provided by several groups. In addition to the studies cited that reported a stimulated vascular renin-angiotensin system in SHRs and in animals with hypertension of renal origin, Okamura et al[83] demonstrated increased vascular CE activity and an enhanced vasoconstrictor response to A-I in arteries isolated from 1-clip, 2-kidney hypertensive rats. Interestingly, the CEI enalapril and an A-II receptor antagonist reduced blood pressure despite the fact that the plasma renin-angiotensin system was not stimulated. This finding adds support to the idea that vascular rather than the plasma renin-angiotensin system stimulation helps to maintain high blood pressure in some forms of hypertension. Results indicating that local vascular A-II generation can be reduced by CEIs in humans have been obtained by Webb and Collier.[84] They reported that during an infusion of ramiprilat, the active parent diacid of ramipril, into the brachial artery of hypertensive patients and normotensive persons, the intrabrachially infused doses of A-I had to be increased by a factor of 20 to obtain the same vasoconstriction as before ramipril, while the vasoconstrictor responses to A-II were not affected by the drug.

Effects unrelated to vascular angiotensin I: Although the data suggested that CEIs may antagonize the vascular renin-angiotensin system locally, interference of these drugs with vascular CE may not only lead to reduced vascular A-II synthesis, but may also have an impact on other local peptide systems, such as kinins, and may alter vascular texture by mechanisms unrelated to CE inhibition. For example, Scherf et al[85] reported a stimulation of prostacyclin synthesis in isolated aortic preparations from rats treated orally with the CEI ramipril, ex vivo, and in aortic tissue exposed to ramiprilat, in vitro. Because aprotinin, a kallikrein inhibitor, attenuated the effect of ramiprilat, the increase in prostacyclin production was interpreted to be due to a CEI-induced accumulation of vascular kinins. However, Oshima et al[86] observed a decrease in aortic prolylhydroxylase, the rate-limiting enzyme of collagen synthesis, after prolonged oral treatment of SHRs with hypotensive doses of captopril. They were unable to demonstrate this effect after single oral captopril administration in SHRs and when aortic tissue from untreated normotensive rats was exposed to captopril in vitro; therefore, they concluded that a reduction in prolylhydroxylase may be ascribed to the hypotensive rather than to direct vascular action of the CEI.

Effects on vascular hypertrophy: In previous morphometric experiments designed to investigate the effects of antihypertensive treatment on vascular hypertrophy, the present investigators observed that normotensive 6-month-old stroke-prone renal hypertensive rats, whose mothers had been treated with an antihypertensive dose of captopril during pregnancy and who had continued to receive captopril until they were killed, exhibited no signs of media hypertrophy to the renal arteries, their branches and resistance vessels (Table I).[87] As in the study by Oshima et al[86] the lack of development of vascular hypertrophy may be explained hemodynamically, i.e., by the failure of these rats to develop hypertension. It is also possible that captopril exerted some direct action on the vascular texture. Thus, further experiments are needed to demonstrate whether chronic CEI treatment alters vascular texture independent of hemodynamic changes and whether this alteration is due to CE inhibition, e.g., suppressed proliferative actions of A-II, or to a nonspecific effect of these drugs unrelated to CE inhibition.

CONCLUSION

In conclusion, there is increasing experimental evidence that the mechanism of action of CEIs involves not only an inhibition of the plasma renin-angiotensin system, but also a local inhibition of CE in various tissues including the heart and the vascular wall. Future research will have to elucidate to which degree a local accumulation of kinins is also involved in the actions of these drugs in addition to reduced local A-II formation. Futhermore, the relative contribution of tissue CE inhibition to the beneficial effects of the CEI in the clinical treatment of various cardiovascular disorders needs to be determined.

REFERENCES

1. Dzau VJ, Ingelfinger JR, Pratt RE. Regulation of tissue renin and angiotensin gene expressions. *J Cardiovasc Pharmacol 1986;8:suppl 10:S11–S16.*
2. Campbell DJ. Tissue renin-angiotensin system: sites of angiotensin formation. *J Cardiovcasc Pharmacol 1987;10:suppl 7:S1–S8.*
3. Lindpaintner K, Jin M, Wilhelm MJ, Suzuki F, Linz W, Schölkens BA, Ganten D. Intracardiac generation of angiotensin and its physiologic role (abstr).

Circulation 1988;77:suppl 1:1–18.
4. Ganten D, Balz W, Hense HW, Schölkens BA, Horstmann G, Lang GE, Unger Th. Characterization and regulation of angiotensin (ANG) peptides in tissue of rabbits and primates (abstr). *J Hypertens 1985;3:suppl 3:S552–S553.*
5. Lindpaintner K, Wilhelm MJ, Jin M, Unger Th, Lang RE, Schölkens BA, Ganten D. Tissue renin-angiotensin systems: focus on the heart. *J Hypertension 1987;5:suppl 2:S33–S38.*
6. Linz W, Schölkens BA, Jin M, Wilhelm M, Ganten D. The heart as a target of converting enzyme inhibitors: studies in ischemic isolated working rat hearts. *J Hypertens 1986;4:suppl 6:S477–S479.*
7. Unger Th, Fleck Th, Ganten D, Lang RE, Rettig R. 2-(N)-(S)-1 Ethoxycarbonyl-3-phenylpropyl-L-alamyl-(1S,3S,5S)-2-azabicyclo (3.3.0)octane-3-carboxylic acid (Hoe 498): antihypertensive action and persistent inhibition of tissue converting enzyme activity in spontaneously hypertensive rats. *Arzneimittelforschung 1984;34(II):1426–1430.*
8. Unger Th, Ganten D, Lang RE, Schölkens BA. Is tissue converting enzyme inhibition a determinant of the antihypertensive efficacy of converting enzyme inhibitors? Studies with the two different compounds, Hoe498 and MK421, in spontaneously hypertensive rats. *J Cardiovasc Pharmacol 1984;6:872–880.*
9. Unger Th, Moursi M, Ganten D, Hermann K, Lang RE. Antihypertensive action of the converting enzyme inhibitor perinodopril (S9490-3) in spontaneously hypertensive rats: comparison with enalapril (MK421) and ramipril (HOE498). *J Cardiovasc Pharmacol 1986;8:276–285.*
10. Heeg E, Meng K, Die Wirkung des Bradykinins, Angiotensins und Vasopressins auf Vorhof, Papillarmuskel, und isoliert durchströmte Herzpräparate des Meerschweinchens. *Naunyn Schmiedebergs Arch Pharmacol 1965;250:35–41.*
11. Freer RJ, Pappanob AJ, Peach MJ, Bing KT, McLean MJ, Vogel S, Sperelakis N. Mechanisms for the positive inotropic effect of angiotensin II on isolated cardiac muscle. *Circ Res 1978;39:178–183.*
12. Kobayashi M, Furkawa Y, Chiba S. Positive chronotropic and inotropic effects of angiotensin II in the dog heart. *Eur J Pharmacol 1978;50:17–25.*
13. Dempsey PJ, McCallum ZT, Kent KM, Cooper T. Direct myocardial effects of angiotensin II. *Am J Physiol 1971;220:477–481.*
14. Koch-Weser J. Myocardial actions of angiotensin. *Circ Res 1964;14:337–342.*
15. Wright GB, Alexander RW, Eckstein LS, Gimbrone MA Jr. Characterization of rabbit ventricular myocardial receptors for angiotensin II: evidence of two sites with different affinities and specificities. *Mol Pharmacol 1984;24:213–221.*
16. Van Gilst WH, De Graeff PA, Kingma JH, Wesseling H, De Langen CDJ. Captopril reduces purine loss and reperfusion arrhythmias in the rat heart after coronary artery occlusion. *Eur J Pharmacol 1984;100:113–117.*
17. De Graeff PA, Van Gilst WH, De Langen CDJ, Kingma JH, Wesseling H. Concentration-dependent protection by captopril against ischemia perfusion injury in the isolated rat heart. *Arch Int Pharmacodyn 1986;280:181–193.*
18. Linz W, Schölkens BA, Han YF. Beneficial effects of the converting enzyme inhibitor, ramipril, in ischemic rat hearts. *J Cardiovasc Pharmacol 1986;8:suppl 10:S91–S99.*
19. Linz W. Schölkens BA. Influence of local converting enzyme inhibition on angiotensin and bradykinin effects in ischemic rat hearts. *J Cardiovasc Pharmacol 1987;10:suppl 7:S75–S82.*
20. Schölkens BA, Becker RHA, Linz W. Pharmakologische Beeinflussung des Konversionsenzyms: Lokale und systemische Effekte an Herz und Gefäßen. *Z Kardiol 1988;77:suppl 3:13–21.*
21. Schölkens BA, Linz W, Lindpaintner K, Ganten D. Angiotensin deteriorates but bradykinin improves cardiac function following ischaemia in isolated rat hearts. *J Hypertens 1987;5:suppl 5:S7–S9.*
22. Schölkens BA, Linz W, König W. Effects of the angiotensin converting enzyme inhibitor ramipril in isolated ischaemic rat heart are abolished by a bradykinin-antagonist. *J Hypertens 1988;6:suppl 4:S25–S28.*
23. Rösen P, Eckel J, Rainauer H. Influence of bradykinin on glucose uptake and metabolism studied in isolated cardiac myocytes and isolated perfused rat hearts. *Hoppe-Seyler's Z Physiol Chem 1983;364:1431–1438.*
24. Schrör K, Metz U, Krebs K. The bradykinin-induced coronary vasodilation. Evidence for an additional prostacyclin-independent mechanism. *Naunyn Schmiedebergs Arch Pharmacol 1979;307:213–221.*
25. Miki M, Ogawa K, Hirata M, Kitaguchi H, Funahara Y. Prostacyclin release from the coronary vascular wall by vasoactive substances. *Thromb Res 1984; 35:665–679.*
26. Van Gilst WH, Van Wijngaarden J, Scholtens E, De Graeff PA, De Langen CDJ, Wesseling H. Captopril-induced increase in coronary flow: an SH-dependent effect on arachidonic acid metabolism. *J Cardiovasc Pharmacol 1987;9: suppl 2:S31–S36.*
27. Raisch RJ, Smith DS, Owen WG. Secretion of plasminogen activator by the isolated perfused rat heart in response to vasoactive agents (abstr). *Thromb Haemost 1985;54:170.*
28. Palmer RMJ, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature 1987;327:524–526.*
29. Carlsson L, Abrahamsson T. Ramiprilat alternates local ischemia induced release of noradrenaline (NA) via a reduction in angiotensin II generation and bradykinin degradation (abstr). *J Mol Cell Cardiol 1988;20:S69.*
30. Xiang J, Linz W, Becker H, Ganten D, Lang RE, Schölkens BA, Unger Th. Effects of converting enzyme inhibitors: ramipril and enalapril on peptide action and sympathetic neurotransmission in the isolated heart. *Eur J Pharmacol 1985;113:215–223.*
31. Freeman GL, Little WC, Haywood JR. Reduction of left ventricular mass in normal rats by captopril. *Cardiovasc Res 1987;21:323–327.*
32. Fernandez PG, Snedden W, Idikio H, Fernandez D, Kin BK, Triggle CR. The reversal of left ventricular hypertrophy with control of blood pressure in experimental hypertension. *Scand J Clin Lab Invest 1984;44:711–716.*
33. Clozel JP, Hefti F. Cilazapril prevents the development of cardiac hypertrophy and the decrease of coronary vascular reserve in spontaneously hypertensive rats. *J Cardiovasc Pharmacol 1988;11:568–572.*
34. Dunn FG, Oigman W, Ventura HO, Messerli FH, Kobrin I, Frohlich ED. Enalapril improves systemic and renal hemodynamics and allows regression of left ventricular mass in essential hypertension. *Am J Cardiol 1984;53:105–108.*
35. Nakashima Y, Fouad FM, Tarazi RC. Regression of left ventricular hypertrophy from systemic hypertension by enalapril. *Am J Cardiol 1984;53:1044–1049.*
36. Linz W, Schölkens BA, Donaubauer HH, Ganten D. Effects of ramipril, nifedipine and dihydralazine on cardiac hypertrophy in rats (abstr). *Clin Exp Hypertens 1988;A10(4):711.*
37. Kromer EP, Riegger AJ. Effects of long-term angiotensin converting enzyme inhibition on myocardial hypertrophy in experimental aortic stenosis in the rat. *Am J Cardiol 1988;62:161–163.*
38. Jackson TR, Blair LAC, Marshall J, Goedert M, Hauley MR. The mas oncogene encodes an angiotensin receptor. *Nature 1988;335:437–440.*
39. The CONSENSUS Trial Study Group. The numerous investigators are listed in the appendix to the paper. Effects of enalapril on mortality in severe congestive heart failure. *N Engl J Med 1987;316:1429–1435.*
40. Romankiewicz JA, Brogden RN, Heel RC, Speight TM, Avery GS. Captopril: an update review of its pharmacological properties and therapeutic efficacy in congestive heart failure. *Drugs 1983;25:6–40.*
41. Captopril Multicenter Research Group I. A placebo controlled trial of captopril in refractory chronic congestive heart failure. *JACC 1983;2:755–763.*
42. Captopril Multicenter Research Group I. A cooperative multicenter study of captopril in refractory chronic congestive heart failure: hemodynamic effects and long-term response. *Am Heart J 1985;110:439–447.*
43. Cleland JGF, Dargie HJ. Heart failure, renal function, and angiotensin converting enzyme inhibitors. *Kidney Int 1987;31:suppl 20:S220–S228.*
44. Dzau VJ. Renal effects of angiotensin-converting enzyme inhibition in cardiac failure. *Am J Kidney Dis 1987;10:74–80.*
45. Lee WH, Packer M. Prognostic importance of serum sodium concentration and its modification by converting enzyme inhibition in patients with severe chronic heart failure. *Circulation 1986;73:257–267.*
46. Packer M. Converting-enzyme inhibition of severe chronic heart failures: views from a skeptic. *Int J Cardiol 1985;7:111–120.*
47. Packer M. Converting-enzyme inhibition in the management of severe chronic congestive heart failure: physiologic concepts. *J Cardiovasc Pharmacol 1987;10:suppl 7:S83–S87.*
48. Pfeffer JM, Pfeffer MA. Angiotensin converting-enzyme inhibition and ventricular remodeling in heart failure. *Am J Med 1988;84:suppl 3A:37–44.*
49. Ryden L. When and how to use angiotensin-converting enzyme inhibition in congestive heart failure. *Am J Cardiol 1988;62:75A–80A.*
50. Ganten D, Hayduk K, Brecht HM, Boucher R, Genest J. Evidence of renin release or production in splanchnic territory. *Nature 1970;226:551–552.*
51. Rosenthal J, Boucher R, Rojo Ortega JM, Genest J. Renin activity in aortic tissue of rats. *Can J Physiol Pharmacol 1969;47:53–56.*
52. Thurston H, Swales JD. Blood pressure response of nephrectomized hypertensive rats to converting enzyme inhibition: evidence for persistent vascular renin activity. *Clin Sci Mol Med 1977;52:299–304.*
53. Thurston H, Swales JD, Bing RF, Hurst BC, Marks ES. Vascular renin-like activity and blood pressure maintenance in the rat: studies of the effect of changes in sodium balance, hypertension and nephrectomy. *Hypertension 1979;1:643–649.*
54. Campbell DJ, Habener JF. Angiotensinogen gene is expressed and differentially regulated in multiple tissues of the rat. *J Clin Invest 1986;78:31–39.*
55. Darby I, Aldred P, Crawford RJ, Fernley RT, Niall HD, Penschow JD, Ryan GB, Coghlan JP. Gene expression in vessels of the ovine renal cortex. *J Hypertens 1985;3:9–12.*
56. Dzau VJ. Vascular angiotensin pathways: a new therapeutic target. *J Cardiovasc Pharmacol 1987;10:suppl 7:S9–S16.*
57. Swales JD, Heagerty AM. Vascular renin-angiotensin system: the unanswered questions. *J Hypertens 1987;5:S1–S5.*
58. Jackson B, Cubela R, Johnston C. Angiotensin converting enzyme (ACE), characterization by I_{25}-MK351A binding studies of plasma and tissue ACE during variation of salt status in the rat. *J Hypertens 1986;4:759–765.*
59. Miyazaki M, Okunishi H, Mishimura K, Toda N. Vascular angiotensin-converting enzyme activity in man and other species. *Clin Sci 1984;66:39–45.*
60. Wilson SK, Lynch DR, Snyder SH. Angiotensin-converting enzyme labelled with ^{3}H-Captopril. Tissue localization and changes in different models of hypertension in the rat. *J Clin Invest 1987;80:841–851.*
61. Okunishi H, Miyazaki M, Okamura T, Toda N. Different distribution of two types of angiotensin II-generating enzymes in the aortic wall. *Biochem Biophys*

Res Comm 1987;149:1186–1192.
62. Velletri P, Bean BL. The effect of captopril on rat aortic angiotensin-converting enzyme. *J Cardiovasc Pharmacol 1982;8:315–325.*
63. Saye JA, Singer HA, Peach MJ. Role of endothelium in conversion of angiotensin I to angiotensin II in rabbit aorta. *Hypertension 1984;6:216–221.*
64. Skidgel RA, Defendini R, Erdös EG. Angiotensin I converting enzyme and its role in neuropeptide metabolism. In: Turner AJ, ed. Neuropeptides and Their Peptidases. *Ellis Horwood VCH, 1988:165–188.*
65. Unger Th, Gohlke P, Ganten D, Lang RE. Converting enzyme inhibitors and their effects on the renin-angiotensin system of the blood vessel wall. *J Cardiovasc Pharmacol 1988;13:suppl 3:S8–S16.*
66. Assad MM, Antonaccio MJ. Vascular wall renin in spontaneously hypertensive rats. *Hypertension 1982;4:487–493.*
67. Unger Th, Hübner D, Schüll B, Lang RE, Rascher W, Retting R, Ganten D. Effect of chronic oral captopril treatment on tissue renin concentration and converting enzyme activity in stroke-prone spontaneously hypertensive rats. In: Rascher W, Clough D, Ganten D, eds. Hypertensive Mechanisms. *Stuttgart, New York: Schattauer Verlag, 1982;768–773.*
68. Cohen ML, Kutz KD. Angiotensin converting enzyme inhibition in tissues from spontaneously hypertensive rats after treatment with captopril or MK-421. *J Pharmacol Exp Ther 1982;220:63–69.*
69. Cohen ML, Wiley KS, Kurz KD. Effect of acute oral administration of captopril and MK-421 on vascular angiotensin converting enzyme activity in the spontaneously hypertensive rat. *Life Sci 1983;32:565–569.*
70. Chevillard C, Brown NL, Mathieu MN, Laliberte F, Worcel M. Differential effects of oral trandolapril and enalapril on rat tissue angiotensin-converting enzyme. *Eur J Pharmacol 1988;147:23–28.*
71. Unger Th, Ganten D, Lang RE. Tissue converting enzyme and cardiovascular actions of converting enzyme inhibitors. *J Cardiovasc Pharmacol 1986b;8:suppl 10:S75–S81.*
72. Nakata K, Nishimura K, Takada T, Ikuse T, Yamauchi H, Iso T. Effects of an angiotensin-converting enzyme (ACE) inhibitor, SA446, on tissue ACE activity in normotensive, spontaneously hypertensive, and renal hypertensive rats. *J Cardiovasc Pharmacol 1987;9:305–310.*
73. Nambu K, Matsumoto K, Takeyama K, Hosoki K, Miyazaki H, Hashimoto M. Tissue levels, tissue angiotensin converting enzyme inhibition and antihypertensive effect of the novel antihypertensive agent alacepril in renal hypertensive rats. *Arzneimittelforschung 1986;36(1):47–51.*
74. Unger Th, Ganten D, Lang RE, Schölkens BA. Persistent tissue converting enzyme inhibition following chronic treatment with Hoe 498 and MK 421 in spontaneously hypertensive rats. *J Cardiovasc Pharmacol 1985;7:36–41.*
75. Longman SD, Howlett DR. Angiotensin-converting enzyme responses following enalapril in the sodium deficient rat. *Eur J Pharmacol 1986;123:379–386.*
76. Nakamura Y, Nakamura K, Matsukura T. Vascular angiotensin converting enzyme activity in spontaneously hypertensive rats and its inhibition with cilazapril. *J Hypertens 1988;6:105–110.*
77. Dzau VJ, Safar ME. Large conduit arteries in hypertension: role of the vascular renin-angiotensin system. *Circulation 1988;77:947–954.*
78. Oliver JA, Sciacca RR. Local generation of angiotensin II as a mechanism of regulation of peripheral vascular tone in the rat. *J Clin Invest 1984;74:1247–1251.*
79. Malik KU, Nasjletti A. Facilitation of adrenergic transmission by locally generated angiotensin II in rat mesenteric arteries. *Circ Res 1976;38:26–30.*
80. Zimmerman BG. Adrenergic facilitation by angiotensin: does it serve a physiological function? *Clin Sci 1981;60:343–348.*
81. Kuriyama S, Nakamura A, Hopp L, Fine BP, Kino M, Cragoe E Jr, Aviv A. Angiotensin II effect on $^{22}Na^{+}$ transport in vascular smooth muscle cells. *J Cardiovasc Pharmacol 1988;11:139–146.*
82. Toda N. Endothelium-dependent relaxation induced by angiotensin II and histamine in isolated arteries of dog. *Br J Pharmacol 1984;81:301–307.*
83. Okamura T, Miyazaki M, Inagami T, Toda N. Vascular renin angiotensin system in two-kidney, one clip hypertensive rats. *Hypertension 1986;8:560–565.*
84. Webb DJ, Collier JG. Vascular angiotensin conversion in humans. *J Cardiovasc Pharmacol 1986;8:suppl 10:S40–S44.*
85. Scherf H, Pietsch R, Landsberg G, Kramer HJ, Düsing R. Converting enzyme inhibitor ramipril stimulates prostacyclin synthesis by isolated rat aorta: evidence for a kinin-dependent mechanism. *Klin Wochenschr 1986;64:742–745.*
86. Oshima T, Matsushita Y, Miyamoto M, Koike H. Effects of long-term blockade of angiotensin converting enzyme with captopril on blood pressure and aortic prolyl hydroxylase activity in spontaneously hypertensive rats. *Eur J Pharmacol 1983;91:283–286.*
87. Henrichs KJ, Unger Th, Berecek KH, Ganten D. Is arterial media hypertrophy in spontaneously hypertensive rats a consequence of or a cause for hypertension. *Clin Sci 1980;59:331S–333S.*

Issues Surrounding a Local Cardiac Renin System and the Beneficial Actions of Angiotensin-Converting Enzyme Inhibitors in Ischemic Myocardium

Charles S. Sweet, PhD

Several experimental in vitro and in vivo studies have shown that structurally diverse converting enzyme inhibitors improve contractile dysfunction, as well as reduce arrhythmia production and acute mortality after occlusion of the coronary artery. Biochemical data have demonstrated that some inhibitors of converting enzyme bind better to cardiac angiotensin-converting enzyme (ACE) than others; however, there has not been any demonstrated correlation between inhibition of the enzyme and improvement in cardiac physiology in the acutely dysfunctioning stunned myocardium. It is assumed that ACE inhibitors reduce tissue generation of angiotensin II; however, this relationship as well as peptide levels in coronary venous effluent need to be specifically measured. The multiple substrates of ACE necessitate further work to explore the role of bradykinin and prostacyclin, which have been implicated by some workers as contributing to the beneficial action of ACE inhibitors. A new question is whether sulfhydryl-containing ACE inhibitors are scavengers of toxic free radicals. Captopril, e.g., has been shown to be a free radical scavenger in superoxide-generating systems. Further work is required; however, as one report has recently shown, captopril does not directly scavenge superoxide but acts indirectly as an antioxidant or by altering the concentration of cytochrome c.

(Am J Cardiol 1990;65:11 I–13 I)

From the Department of Pharmacology, Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania.

Address for reprints: Charles S. Sweet, PhD, Department of Pharmacology, Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486.

Pharmacologic approaches that alter the course of myocardial damage associated with occlusion and reperfusion of the coronary artery are of interest. Over the last several years it has become clear that, under appropriate experimental conditions of myocardial ischemia, angiotensin-converting enzyme (ACE) inhibitors can ameliorate malignant arrhythmias, improve contractile dysfunction and limit infarct size. To explain the mechanism of action of these drugs in ischemic injury, it may be necessary to invoke 2 controversial theories: the tissue renin-angiotensin system and the oxygen-derived free radical hypothesis. Issues in this area of research are (1) the physiologic importance of the cardiac renin system, i.e., whether angiotensin II plays a deleterious role in the extension of ischemic injury; (2) whether converting enzyme inhibitors, in therapeutically meaningful concentrations, can limit the cardiac generation of angiotensin II, improve contractile function and arrhythmia production; and (3) whether ACE inhibitors can limit the production of sequester toxic free radicals. The purpose of this review is to briefly analyze the experimental evidence that ACE inhibitors can limit ischemic injury in vitro and in vivo.

CARDIAC PHARMACOLOGY OF ANGIOTENSIN

Angiotensin II has been evaluated extensively as a peripheral vasoconstrictor and mediator of aldosterone release. Angiotensin's effect on the heart[1–3] and coronary circulation[4] are not particularly striking at physiologic concentrations. Pharmacologic concentrations of angiotensin II, under some conditions, can increase contractility in vitro[1,2]; however, the positive inotropy observed in the isolated myocardium is outweighed in the intact heart by negative inotropic influences.[3] High affinity binding sites for angiotensin II in the ventricle have been described by using radioligand binding techniques.[5] These studies and others, suggesting the presence of a local renin system in the heart, have renewed the interest in cardiac actions of angiotensin II.

LOCAL CARDIAC RENIN SYSTEM

The renin-angiotensin system was originally conceived as a classic endocrine system with the peptide angiotensin II being transported to its target sites through the blood. The concept of a tissue renin system has gained momentum in recent years, in part because of the expression of the relevant genetic information for renin and

angiotensinogen in the heart.[6–10] Furthermore, a physiologically active pathway for the in vitro conversion of angiotensin I to angiotensin II has been clearly demonstrated in experiments in which dose-dependent ACE inhibitors suppressed angiotensin II generation in vitro using a sensitive radioimmunoassay.[11]

Some studies have estimated the percent inhibition of cardiac ACE after oral administration of a number of structurally diverse inhibitors of this enzyme.[12,13] In these ex vivo experiments, hearts are removed after oral dosing and ACE levels are estimated in homogenates. In interpreting these data, it is important to realize that when tissue samples are diluted into the assay incubation mixture, the degree of inhibition ex vivo will be less than that which existed in vivo. Furthermore, a functional consequence of the inhibition of cardiac ACE has not been reported. Cohen and Kurz[12] showed that ACE activity in the heart was low relative to the lung and aorta, but that both captopril and enalapril produced significant inhibition of the enzyme in the hearts of spontaneously hypertensive rats. In a more extensive study, Cushman et al[13] found striking differences between ACE inhibitors with regard to their ability to inhibit cardiac ACE. For example, enalapril and ramipril, 2 drugs shown to exert cardioprotective effects, produced only slight inhibition of cardiac ACE which lasted for 1 hour. In the absence of functional data, it will not be apparent whether blockade of cardiac ACE is a prerequisite for "cardioprotection," or is a general phenomenon of this class of drugs regardless of whether they display a prominent degree of cardiac tissue selectivity.

In summary, the physiologic function of angiotensin in the heart can only be speculated at this time. Angiotensin may have a role in the regulation of cardiac contractility (because of its positive inotropic effect), may have a potential role in the regulation of cellular metabolism (assumed because of angiotensin binding sites on mitochondria), and may have mitogenic effects (which could be important in ventricular hypertrophy). The participation of angiotensin II, either directly or indirectly, in myocardial ischemia has received recent attention in several laboratories that have demonstrated a protective effect of ACE inhibitors in vitro or ex vivo after occlusion of the coronary artery.[11,14–17]

IN VITRO EFFECTS OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS IN RAT HEARTS

vanGilst et al[14] demonstrated that a very large dose of captopril in vitro (Langendorff isolated heart) protected myocardial cells damaged by reperfusion and reduced (40%) purine overflow. Importantly, the mechanical function impaired by ischemia and reperfusion improved with captopril and reperfusion-induced fibrillation lessened in hearts treated with captopril.

Other structurally diverse ACE inhibitors (ramapril and enalapril) have also been studied in isolated hearts.[15–17] For example, direct evidence for cardiac ACE inhibition was provided by Xiang et al[15] who demonstrated that converting enzyme activity was markedly reduced after oral treatment with ACE inhibition, persisting for up to 24 hours after a single dose. Furthermore, the effects of stimulation of the sympathetic nerve supply were blunted with oral pretreatment with ramapril, suggesting that local cardiac ACE may be involved in angiotensin-mediated facilitation of neurotransmission.

As an extension of their earlier work, vanGilst et al[16] showed that the active inhibitor of HOE-498 (ramiprilat), a nonsulfhydryl ACE inhibitor, reduced the incidence and duration of ventricular fibrillation caused by reperfusion after 15 minutes of local ischemia. Predictably, the pro-drug enalapril was not active in this model. Both captopril and ramiprilat abolished the norepinephrine overflow associated with reperfusion. Because indomethacin abolished the effects of captopril, the ACE inhibitors may have reduced catecholamine overflow indirectly by a stimulation of prostacyclin synthesis.

Another beneficial effect of ACE inhibitors is their ability to vasodilate the coronary circulation. In one study, captopril, zofenoprilat and ramiprilat increased coronary blood flow in vitro, but only ramiprilat did so by increasing prostacyclin synthesis. It has been suggested that this response was mediated by an increase in endogenous bradykinin.[17] Indomethacin did not block the coronary vasodilating effects of 2 sulfhydryl-containing inhibitors, although previous work[16] has demonstrated that an indomethacin-sensitive mechanism was involved in the catecholamine overflow response.

The concentration of ACE inhibitor used in many in vitro studies is substantially above that needed to inhibit plasma/pulmonary converting enzyme in vitro. The fact that it is possible to demonstrate cardiac ACE inhibition in tissues that are removed from rats pretreated with oral ACE inhibitors suggests that the heart can take up sufficient drug to inhibit tissue-converting enzyme. However, the measurement of tissue drug levels in all of these experiments has not been undertaken.

Taken together, these in vitro and ex vivo studies in the ischemic rat heart demonstrate that ACE inhibitors, although at often high concentrations, can ameliorate cardiac mechanical function, improve coronary blood flow, reduce reperfusion arrhythmias, lessen the loss of cardiac high energy phosphates, and attenuate the deleterious effects of catecholamines. It is noted that these effects do not appear to be limited to a single chemical class of compounds.

IN VIVO EFFECTS OF ANGIOTENSIN-CONVERTING ENZYME INHIBITION IN MODELS OF OCCLUSION/REPERFUSION

The potential role of angiotensin II in the myocardial stunning and arrhythmia production that accompanies reperfusion has become the focus of interest in several laboratories using both canine and rat models of ischemia and are discussed in the next section.

Canine models of ischemia: ACE inhibitors have been given to dogs before occlusion of the left anterior descending artery in an attempt to reduce the severity of the ischemic injury during the occlusion period in anticipation that it would reduce the incidence of arrhythmias

during the subsequent reperfusion period.[18,19] The vasodilator drugs felodipine (calcium entry blocker) and ketanserin (serotonin and α_1 blocker) were compared with captopril and enalapril in one study. All compounds were administered so they would reduce mean arterial pressure by about 25%. Although all of the compounds reduced the incidence of premature ventricular depolarizations during the occlusion period, only enalapril significantly lowered the incidence of ventricular fibrillation (6 of 9 dogs fibrillated with placebo; 1 of 9 given enalapril). Estimates of myocardial stunning were not reported.

Using a shorter occlusion period, Westlin and Mullane[19] found that captopril, but not enalaprilat, alleviated the postischemic contractile impairment of the left ventricle indicating that this response was independent of ACE inhibition. Presumably, both compounds worked beneficially to improve the myocardial oxygen supply/demand ratio. When captopril was given immediately before reperfusion, it improved contractile dysfunction to a similar extent as when administered before occlusion. This observation would indicate that captopril works on a mechanism (scavenging free radicals?) related to reperfusion as opposed to the ischemic event. Westlin and Mullane[19] showed in 3 in vitro systems that captopril is a scavenger of the superoxide ion. Kukreja et al[20] indicated, however, that this effect was highly dependent on the concentration of cytochrome c. In another in vitro assay (autoxidation of epinephrine), the same investigators showed that captopril may have acted as an antioxidant.

Interestingly, the incidence of ventricular fibrillation in rats occurred in 6 of 16 in the control group, 0 of 13 in the captopril group, and in 1 of 11 in the enalaprilat group.[14] In the Elfellah and Ogilvie study,[18] captopril was given intravenously at 0.5 mg/kg as opposed to the higher dose (intravenously at 5 mg/kg) used by Westlin and Mullane.[19] Dose differences may explain the failure of captopril to improve the incidence of ventricular fibrillation, or some other protocol difference; e.g., anesthesia and duration of occlusion may explain the discrepancy and remains to be determined.

In a protocol that used a 60-minute period of occlusion followed by reperfusion, Liu et al[21] showed that 6 of 14 control dogs died after occlusion of the left anterior descending artery and 4 of the remaining 8 died during reperfusion, whereas only 1 of 10 dogs died in the enalapril group (none during reperfusion). Unlike the Westlin study,[19] the segmental contraction of the ischemic area was improved by enalapril.[21]

Rat models of ischemia: As predicted from in vitro effects in rat hearts, ACE inhibitors are beneficial in vivo in the rat model of ischemia (total occlusion protocol). For example, 3 ACE inhibitors (captopril, enalapril and perindopril) at 2 to 3.5 mg/kg reduced blood pressure and heart rate when given before occlusion of the coronary artery. The total duration of ventricular fibrillation and overall mortality was reduced by the 3 ACE inhibitors.[22]

In a global ischemia protocol, enalapril, given twice within 24 hours before coronary occlusion (no reperfusion), reduced both the serum creatine phosphokinase levels and the electrocardiographic signs of ischemia, compared with control rats treated with vehicle.[23] Left ventricular free wall creatine phosphokinase changes in rats treated with enalaprilat have been reported by Hock et al.[24] When measured 48 hours after occlusion, enalaprilat significantly blunted the reduction in free wall loss of creatine phosphokinase.

REFERENCES

1. Fowler NO, Holmes JC. Coronary and myocardial actions of angiotensin. *Circ Res 1964;14:191–201.*

2. Koch-Weser J. Nature of inotropic action of angiotensin. *Circ Res 1965; 16:230–237.*

3. Ahmed SS, Levinson GE, Weisse AB, Regan TJ. The effect of angiotensin on myocardial contractility. *J Clin Pharmacol 1975;15:276–285.*

4. Siegl PKS, Sweet CS. Angiotensin converting enzyme inhibitors and coronary blood flow: a review of preclinical and clinical studies. *Curr Opinion Cardiol, in press.*

5. Wright GB, Alexander RW, Ekstein LS, Gimbrone MA. Characterization of the rabbit ventricular myocardial receptor for angiotensin II. *Mol Pharmacol 1983;24:213–221.*

6. Dzau VJ, Re RN. Evidence for the existence of renin in the heart. *Circulation 1987;75:1134–1136.*

7. Dzau VJ. Circulating versus local renin-angiotensin system in cardiovascular homeostasis. *Circulation 1988;7:14–113.*

8. Lindpaintner K, Wilhelm MJ, Jin M, Unger T, Lang RE, Schoelkens BA, Ganten DJ. Tissue renin-angiotensin systems: focus on the heart. *Hypertension 1987;5:S33–S38.*

9. Lindpaintner K, Jin M, Wilhelm MJ, Suzuki F, Linz W, Schoelkens BA, Ganten D. Intracardiac generation of angiotensin and its physiologic role. *Circulation 1988;77:118–123.*

10. Suzuki F, Hellmann T, Murakami K, Ludwig G. Expressions of the genes for renin and angiotensinogen in tissues of rats. *Naunyn-Schmiedebergs Arch Pathol 1987;335:R66–R71.*

11. Linz H, Scholkens BA, Han YF. Beneficial effects of the converting enzyme inhibitor, ramipril, in ischemic rat hearts. *J Cardiovasc Pharmacol 1986;8:S91–S99.*

12. Cohen ML, Kurz KD. Angiotensin converting enzyme inhibition in tissues from spontaneously hypertensive rats after treatment with captopril or MK-421. *J Pharmacol Exp Ther 1982;220:63–69.*

13. Cushman DW, Hang FL, Fung WC, Harvey CM, DeForrest JM. Differentiation of angiotensin-converting enzyme (ACE) inhibitors by their selective inhibition of ACE in physiologically important target organs. *Am J Hypertens 1989;2:294–306.*

14. vanGilst HH, deGraeff PA, Kingma JH, Hessling H, deLangen CDJ. Captopril reduced purine loss and reperfusion arrhythmias in the rat heart after coronary artery occlusion. *Eur J Pharmacol 1984;100:113–117.*

15. Xiang JZ, Linz W, Becker H, Ganten D, Lang RE, Scholkens B, Unger T. Effects of converting enzyme inhibitors: ramipril and enalapril on peptide action and sympathetic neurotransmission in the isolated heart. *Eur J Pharmacol 1985;113:215–223.*

16. vanGilst HH, deGraeff PA, Wesseling H, deLangen CDJ. Reduction of reperfusion; arrhythmias in the ischemic isolated rat heart by angiotensin converting enzyme inhibitors: a comparison of captopril, enalapril and HOE 498. *J Cardiovasc Pharmacol 1986;8:722–728.*

17. vanGilst WH, Scholtens E, deGraeff PA, deLangen CDJ, Wesseling H. Differential influences of angiotensin converting enzyme inhibitors on the coronary circulation. *Circulation 1988;77:124–129.*

18. Elfellah MS, Ogilvie RI. Effect of vasodilator drugs on coronary occlusion and reperfusion arrhythmias in anesthetized dogs. *J Cardiovasc Pharmacol 1985;7:826–832.*

19. Westlin W, Mullane K. Does captopril attenuate reperfusion-induced myocardial dysfunction by scavenging free radicals? *Circulation 1988;77:130–139.*

20. Kukreja RC, Kontos HA, Eaton LR, Hess ML. Captopril and enalaprilat do not scavenge the superoxide anion. *Am J Cardiol 1990;65:24 I–27 I.*

21. Liu LY, Chen X, Li K, Wu HJ. Beneficial effects of enalapril on reperfusion arrhythmia and segmental contraction in anesthetized dogs. *Acta Pharmacol Sin 1987;434–438.*

22. Ribuot C, Rochette L. Converting enzyme inhibitors (captopril, enalapril, perindopril) prevent early post-infarction ventricular fibrillation in the anesthetized rat. *Cardiovasc Drug Ther 1987;1:51–55.*

23. Li K, Chen Xiu. Protective effects of captopril on myocardial ischemia and reperfusion damage of rat. *J Mol Cell Cardiol 1987;19:909–915.*

24. Hock CE, Ribeiro LGT, Lefer AM. Preservation of ischemic myocardium by a new converting enzyme inhibitor, enalaprilic acid, in acute myocardial infarction. *Am Heart J 1985;109:222–228.*

Myocardial Ischemia, Reperfusion and Free Radical Injury

Benedict R. Lucchesi, PhD, MD

Reperfusion of coronary arteries to limit myocardial ischemic injury and extent of myocardial necrosis is possible by either the use of fibrinolytic therapy, coronary angioplasty or coronary artery bypass surgery. The concept that early reperfusion may salvage jeopardized myocardium is derived from basic experimental studies which purported to demonstrate that the ultimate extent of irreversible myocardial injury could be reduced by reperfusion of the ischemic myocardium within 3 hours from the onset of regional myocardial ischemia. It is firmly established that salvage of ischemic myocardium is dependent on early restoration of blood flow to the myocardium at risk. Despite dependency on reoxygenation for ultimate survival, myocardial tissue that is reperfused and reoxygenated may be subjected to additional injurious insult due to reactive metabolites of oxygen. The cytotoxic species of oxygen are referred to as "oxygen free radicals." Coincident with the influx of inflammatory cells into the reperfused region is an additional loss of otherwise viable myocardial cells. There is strong support for the concept that the polymorphonuclear leukocyte is a contributor to the phenomenon of "reperfusion" or "reoxygenation" injury in the blood perfused heart. This discussion focuses on the role of the neutrophil as a potential contributor to the extension of tissue injury and reviews those interventions, which although in the experimental stage, offer promise of becoming therapeutically important in the future and may help elucidate the mechanisms underlying the potentially deleterious role of the neutrophil in situations involving whole blood reperfusion of the ischemic myocardium.

(Am J Cardiol 1990;65:14 I–23 I)

It is recognized that prolonged myocardial ischemia is accompanied by a time-dependent loss of the viability of myocardial cells in the jeopardized region of the heart.[1] Reperfusion is necessary to initiate and maintain those functions responsible for reversal of the changes induced by ischemia and for the continued survival of the myocardial cells at risk of permanent damage. The development of pharmacologic methods for reperfusion of the ischemic heart has reduced mortality and has led to the acceptance of thrombolytic therapy as the standard approach to the management of patients with an evolving acute myocardial infarction.[2]

Reperfusion injury has been recognized as occurring in experimental models of myocardial ischemia.[3] It has been assumed that the observed loss of cell viability associated with the reintroduction of oxygen was solely an acceleration of cell death in myocytes that were beyond the point of salvage, or had been injured irreversibly. Reexamination of this question suggests that reperfusion of the previously ischemic heart with oxygenated whole blood may be detrimental as well as beneficial to the myocyte.[4–6] A significant effort has been devoted to gaining a better understanding of the oxygen paradox[7] or the phenomenon of reperfusion injury,[7,8] or both, which may be more appropriately referred to as reoxygenation injury (i.e., an extension in the loss of myocardial cell viability beyond that due to the ischemic process itself). A number of recent reviews have been devoted to an examination of the question of whether reactive species of oxygen, or oxygen free radicals, contribute to the development of irreversible myocardial cell injury during the period of reperfusion.[7–10] The purpose of this essay is to focus attention on the role of the polymorphonuclear leukocyte (PMN) as a contributor to the phenomenon of reperfusion injury and to call attention to factors that modulate the inflammatory response to myocardial cell injury.

NEUTROPHIL-DEPENDENT DAMAGE TO THE ENDOTHELIUM AND CARDIAC MYOCYTE

One of the important functions of the PMN is defense of the host organism. However, during altered physiologic states, the PMN may react in a manner that leads to tissue injury. The tissue damage resulting from myocardial ischemia activates a sequence of events characterized as an inflammatory response that occurs independently of any improvement in myocardial reoxygenation. The concept we propose is that the invading leukocytes and ensuing inflammatory response contributes to the extension of myocardial cell injury adding to the irreversible cell injury from the ischemia itself. Interventions directed against the inflammatory cells and the cytotoxic products produced at the site of myocardial injury may result in a

From the University of Michigan Medical School, Department of Pharmacology, Ann Arbor, Michigan. This study was supported by Grant HL-19782-11 from the National Heart, Lung, and Blood Institute, the National Institutes of Health, Bethesda, Maryland.

Address for reprints: Benedict R. Lucchesi, PhD, MD, The University of Michigan Medical School, Department of Pharmacology, M-6322 Medical Science Building I, Ann Arbor, Michigan 48109-0626.

reduction in the extent of tissue damage associated with myocardial ischemia or reperfusion, or both. The circulating PMN does not interact with the normal endothelial surface of the vasculature. However, the PMN can be activated in response to stimuli arising from the ischemic insult, either from within or outside of the vascular compartment, and can be induced to undergo shape changes and ultimately to adhere to the surface of the vascular endothelium.[11]

Infiltration of the ischemic myocardium by PMNs begins within 60 minutes of the onset of regional myocardial ischemia and increases progressively after the onset of reperfusion.[12–14] Neutrophils invade the region of ischemic myocardium long before the transmural progression of irreversible injury reaches the subepicardial myocardial region.[15] Reperfusion is essential to prevent further extension of ischemia-induced myocyte necrosis. In the absence of reperfusion, the slowly developing inflammatory response to tissue injury permits neutrophil-mediated injury to progress and requires 12 hours or more to become manifest by histologic examination of myocardial tissues. Factors involved in the initiation and termination of the myocardial inflammatory response are not understood in detail, but serve as an interesting target for the development of new therapeutic interventions to prevent extension of tissue injury, either during the ischemic period or shortly after reperfusion.

A number of studies[9–16] have demonstrated that interventions that limit neutrophil function or interfere with the cytotoxic factors produced by the infiltrating phagocytic cells can reduce ultimate infarct size in experimental animals that have undergone a period of regional myocardial ischemia followed by reperfusion. The role of the neutrophil as a contributor to myocardial injury in response to ischemia was suggested initially in 1975.[17] Direct studies have demonstrated that ultimate infarct size was reduced by 43% in the canine heart under conditions of neutropenia, compared with control animals subjected to 90 minutes of regional myocardial ischemia followed by reperfusion for 6 hours.[5] This observation subsequently was confirmed by other investigators using alternative means of inducing neutropenia.[6]

Additional support for the concept of neutrophil-mediated myocardial injury is derived from the pharmacologic modulation of neutrophil function during myocardial ischemia and reperfusion. Recognition of the mechanism of protection provided by ibuprofen on experimental myocardial injury was an important step in addressing the role of the neutrophil in promoting reperfusion injury. Ibuprofen, in contrast to other inhibitors of cyclooxygenase, such as indomethacin and aspirin,[18,19] possess myocardial protective properties without altering myocardial blood flow or the relationship between myocardial oxygen supply and demand.[20,21] A review of several studies indicated that of the nonsteroidal anti-inflammatory agents examined, only ibuprofen reduced neutrophil infiltration to the reperfused myocardium. This observation suggests that the PMN contributes to the extension of tissue injury on reperfusion[5,6] and is in keeping with the original findings of Hill and Ward.[17] Neither aspirin nor indomethacin reduced infarct size or the in vitro neutrophil respiratory burst in response to stimulation of the PMN with C_{5a}. Ibuprofen, however, prevented the complement induced activation of the PMN and the production of oxygen radicals.[19] It is possible to conclude that ibuprofen, a nonsteroidal anti-inflammatory agent, does not exert its protective effect on the myocardium through inhibition of the cyclooxygenase pathway of arachidonic acid metabolism, or by altering factors that restore the balance between myocardial oxygen supply and demand.

Additional evidence for the role of the PMN as a mediator of reperfusion injury was obtained from studies in which prostacyclin, or a related analog, iloprost, as well as prostaglandin E_1, limited ultimate infarct size in a canine model of regional ischemia and reperfusion. The mechanism of action was attributed to the ability of the prostanoids to inhibit the formation and release of neutrophil-derived cytotoxic metabolites of oxygen.[22–24] Evidence from a number of studies indicates that the pharmacologic inhibition of neutrophil function correlates with the observed beneficial effects on myocardial reperfusion injury.

CHEMOTACTIC FACTORS AND THE ACTIVATION AND RECRUITMENT OF NEUTROPHILS

The complement system serves as one of the most important sources of inflammatory mediators involved in the acute inflammatory response. Complement activation generates a potent neutrophil chemotactic factor, C_{5a}. This anaphylatoxin has a role in the recruitment of PMNs to the site of tissue injury and in their activation. Proteolytic enzymes from the plasma and cellular sources react with individual complement components resulting in the localized formation of inflammatory mediators, without causing a generalized activation of the complement cascade. The presence of a tissue protease in the ischemic myocardium was suggested initially as being involved in cleaving the third component of complement into chemotactically active fragments that may stimulate the attraction of neutrophils to the myocardium.[25,26] Cardiac lymphatic drainage from the ischemic myocardium contains molecules of mitochondrial and subcellular origin that are bound to $C1_q$, which may activate the complement cascade, promote the release of leukotactic anaphylatoxins, and stimulate the migration of PMNs to sites of tissue injury.[27] Depletion of complement with cobra venom factor significantly reduced PMN infiltration into ischemic myocardium and resulted in a decrease in tissue injury associated with regional ischemia and reperfusion.[25,28] Complement-derived products can exacerbate ischemic tissue injury and cardiac dysfunction through mechanisms that are independent of the presence of neutrophils. Neutrophil-independent injury by complement may be associated with the vascular actions of the C_{3a}, C_{4a} and C_{5a}, known to enhance vascular permeability and alter vessel tone. Furthermore, tissue injury may be a consequence of the formation of cytolytic membrane attack complex ($C_{5b\text{-}9}$), which can result in the production of transmembrane channels and facilitate the influx of extracellular calcium and disruption of myocyte function.[29]

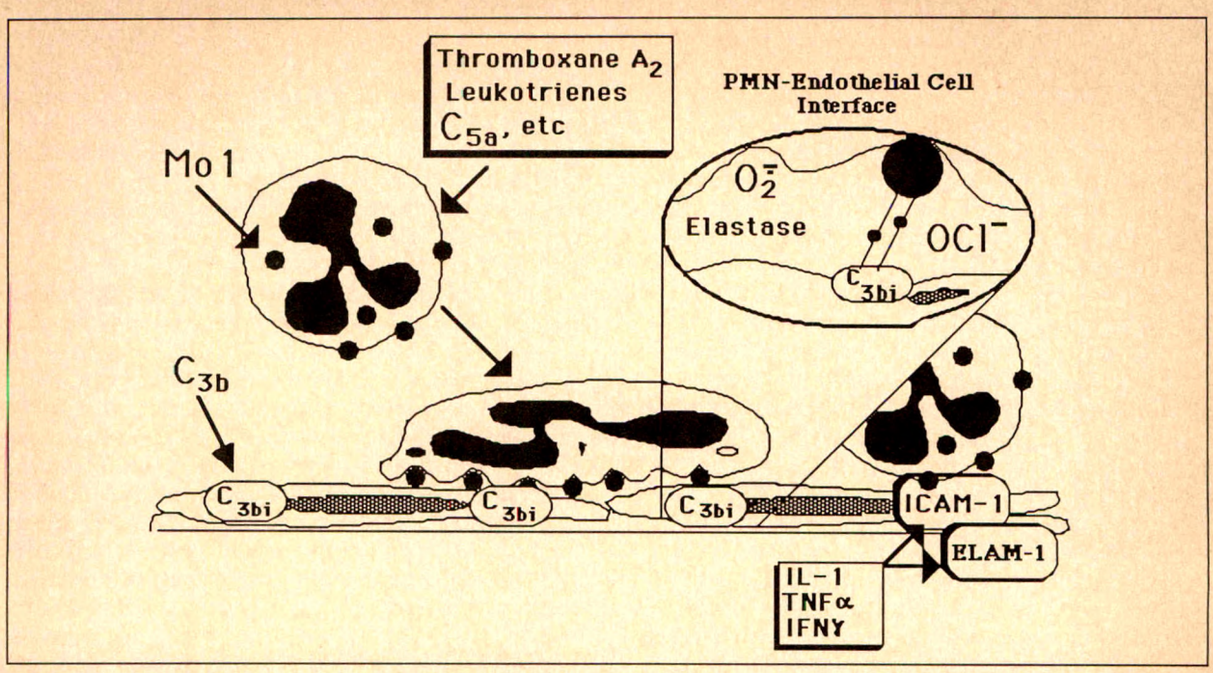


FIGURE 1. Representation of the leukocyte-endothelial cell interaction in response to injury. Endothelial injury secondary to ischemia and reoxygenation promotes neutrophil adherence to the cell surface. Endothelial cell surface molecules interact with neutrophil CD18 glycoprotein adhesion-promoting receptor. C_{3bi} derived from the activation of the complement system in response to injury serves to "opsonize" the endothelial cell and is the ligand for Mo1 expressed on the surface of the neutrophil. Expression of the neutrophil CD11b/CD18 heterodimeric complex (Mo1) on the plasma membrane of the neutrophil is a response to inflammatory stimuli (C_{5a}, leukotrienes, thromboxane, etc.). Neutrophil CD18 molecules can interact with intracellular adhesion molecule-1 (ICAM-1) on the endothelial cell membrane thereby serving as an alternate mechanism for the attachment of inflammatory cells to a target tissue. ICAM-1 and ELAM-1 (endothelial leukocyte adhesion molecule) are expressed in response to a variety of cytokines acting on the endothelial cell. In addition, the cytokines, interleukin-1 (IL-1), tumor necrosis factor (TNF) and interferon γ (IFN γ) will induce synthesis and secretion of a neutrophil chemotactic factor by endothelial cells, thus permitting the endothelium to participate actively in the recruitment and attachment of inflammatory cell mediators to the tissue that has been "targeted" as a result of injury. Whether the sequence of events described occurs in the heart that has been subjected to ischemia and reperfusion remains a topic of further study.

Endothelial cells may be an important source of a specific neutrophil chemotactic factor.[30] Either interleukin-1 (IL-1) or tumor necrosis factor α (TNF-α) will induce, in endothelial cells, the synthesis and secretion of a neutrophil chemotactic factor similar in structure to a human monocyte-derived neutrophil-activating factor. Neutrophil-activating factor will promote neutrophil chemotaxis and, in addition, will induce an increase in intracellular calcium, an oxidative burst, and granule exocytosis through a guanosine triphosphate–binding protein-dependent pathway. Similar responses are observed with other chemotactic peptides (e.g., C_{5a}, formyl-methionyl-leucyl-phenylalanine).[31] The role that endothelial cell-derived mediators may play in activating neutrophils after ischemic injury has not been investigated. These relationships are important in determining the mechanisms that initiate the activation of circulating neutrophils and promote their adherence to the injured vascular wall.

ADHERENCE-PROMOTING CELL SURFACE GLYCOPROTEIN COMPLEXES AND THE INTERACTION BETWEEN THE GRANULOCYTES AND ENDOTHELIAL CELLS

Granulocytes migrate across the vascular endothelium into the extravascular space in response to tissue injury. Initially, the inflammatory cells adhere to the vascular endothelial cell. A family of heterodimeric glycoproteins, possessing a common β subunit of 95 kDa (CD18) associated noncovalently with separate α subunits of 177, 165 and 150 kDa, are present on the neutrophil. The neutrophil surface glycoproteins are designated as lymphocyte function-associated antigen-1 (LFA-1) (CD11a), Mo1 or Mac-1 (CD11b) and gp150,95 (CD11c), respectively. The Mo1 glycoprotein heterodimer is involved in the process of cellular adhesion and serves as the receptor for C3bi opsonized particles.

Distinct stimuli mobilize Mo1 from intracellular sites and lead to its expression on the cell surface. Mo1 participates in adherence of the leukocyte to the endothelial cell and to other PMNs, as well as in chemotaxis and spreading on cell surfaces. An increase up to twofold in Mo1 cell-surface expression has been observed. At least 50% of the total population of Mo1 receptors is located intracellularly. The increased expression of Mo1 increases neutrophil adherence to cell surfaces and facilitates chemotaxis. The increase in Mo1 glycoprotein expression is coupled to the release of neutrophil gelatinase which participates in the degradation of connective tissue, thus allowing for the passage of neutrophils through capillary walls and into the extravascular space. The up-regulation

of Mo1, for which C3bi serves as the ligand, would allow for enhanced recognition and attachment to endothelial surfaces that have been "opsonized." Injury to the endothelium from ischemia and reoxygenation promotes neutrophil adherence to the cell surface. There is enhanced binding of neutrophils to endothelial surfaces secondary to the interaction of neutrophil CD18 molecules with the intercellular adhesion molecule-1 (ICAM-1) on the endothelial cell membrane.[32] Enhanced ICAM-1 expression on the endothelial cell surface can be induced by multiple inflammatory mediators including bacterial endotoxin and the cytokines IL-1, interferon-γ, and TNF-α.[33] A distinct endothelial leukocyte adhesion molecule (ELAM-1) that promotes neutrophil binding to the endothelium can be induced by specific cytokines.[34] Whether a similar increase in the expression of ELAM-1, ICAM-1 or ICAM-1-like molecules occurs in ischemic endothelium is not known, but may play an important role in leukocyte localization to ischemic myocardium (Fig. 1).

It has been observed that specific cytokines will induce synthesis and secretion of a neutrophil chemotactic factor by endothelial cells. This observation and studies cited provide further evidence for an active role of the endothelial cell in modulating neutrophil activation and recruitment to ischemic tissues, rather than a "passive" participant in the interaction of inflammatory cells with the vascular wall. The interaction between endothelial cells and PMNs is required for an effective chemotactic response and for some forms of neutrophil-mediated vascular injury. This represents an important initial step in the sequence of events associated with the acute inflammatory response. A variety of agonists involved in acute inflammation, including thrombin, platelet-activating factor and leukotriene C_4, are known to facilitate the adherence of neutrophils to the endothelial surface.

The neutrophil CD18 glycoprotein molecules may participate in other functions beside cell adhesion and chemotaxis. The glycoproteins may be important in the transduction of signals from the cell surface to intracellular enzymatic regulatory systems as suggested by the presence of an extensive intracellular domain providing sites for interaction with cytoplasmic proteins and cytoskeletal elements.

Monoclonal antibodies, specific for either the α or β subunits of Mo1, inhibit certain neutrophil/monocyte functions, such as the binding of C3bi-opsonized particles, and adhesive interactions of neutrophils and monocytes, including neutrophil aggregation, monocyte/neutrophil adhesion and spreading on substrates (including vascular endothelium), and chemotaxis. The leukocytes of patients who are genetically deficient in their expression of the Mo1 glycoprotein exhibit an impairment of C3bi-particle binding and leukocyte adhesive interactions. The Mo1 glycoprotein has a domain that functions as the plasma membrane receptor for C3bi(CR3). The critical role of neutrophil glycoprotein adhesive receptors Mo1 in the inflammatory response of activated neutrophils is illustrated by the inhibitory effect of specific monoclonal antibodies on neutrophil-mediated endothelial cell injury in a rat lung model of adult respiratory distress syndrome[35] and neutrophil-dependent vascular injury in skin.[36]

A monoclonal antibody (904) that binds to the Mo1 leukocyte cell adhesion-promoting glycoprotein CD11b/CD18 was administered to open-chest anesthetized dogs 45 minutes after the induction of regional myocardial ischemia. Ischemia was produced by occluding the left circumflex coronary artery for 90 minutes followed by reperfusion for 6 hours. There was no difference between control and antibody-treated groups with respect to arterial blood pressure, heart rate or coronary blood flow. Administration of antibody produced no observable effect on circulating neutrophil counts demonstrating that antibody-bound neutrophils were not cleared from the circulation. Myocardial infarct size, expressed as a percentage of the area at risk of infarction, was reduced by 46% with anti-Mo1 treatment. The area at risk of infarction was similar between groups. Accumulation of neutrophils within the myocardium was reduced significantly with anti-Mo1 treatment.[37,38] Similar protective effects were obtained in subsequent studies with anti-Mo1 F(ab′)2 fragments in which antibody treatment was maintained for 48 hours into the reperfusion period and infarct size was determined at 72 hours after reperfusion. Figure 2 summarizes the results from studies in which treatment with anti-Mo1 antibody was associated with a significant protective effect regardless of whether infarct size was determined after 6 or 72 hours of reperfusion. Furthermore, regional myocardial blood flow determinations indicated that both groups had equal degrees of ischemia in the inner two-thirds of the myocardium during the period of coronary artery occlusion. Results with the anti-Mo1 antibody indicated that the adhesive interactions of the neutrophil played a central role in neutrophil-mediated damage and that inhibition of neutrophil adhesive interactions can reduce the extent of irreversible myocardial damage associated with reperfusion. The results are in accord with earlier studies in which myocardial reperfusion injury was reduced by a variety of interventions that shared one common property; i.e., they altered the ability of the neutrophil to react with its target tissue, the ischemically altered myocardial cell.[24,39–41]

The relative contribution of Mo1, LFA-1 and p150,95 to leukocyte endothelial adhesion is dependent on the applied stimulus and the particular inflammatory cell involved. Monocytes and granulocytes employ distinct subunits of the adhesion-promoting glycoproteins when they interact with the vascular endothelium. Mo1, as well as LFA-1 and p150,95, molecules have been shown to be involved in leukocyte-endothelial cell adhesion. The adhesion may be prevented by antibodies directed against the specific portion of the heterodimeric surface molecules.[42] Granulocyte adhesion to endothelial cells, by means of the CD11/CD18 subunits, varies according to the activation state of the granulocyte and endothelial cell. It is reported that granulocyte adhesion, promoted by activation of the inflammatory cells with PMA, was mediated primarily by Mo1 and that the adhesion was not inhibited by antibodies directed against LFA-1 or p150,95. Exposure of endothelial cells to recombinant

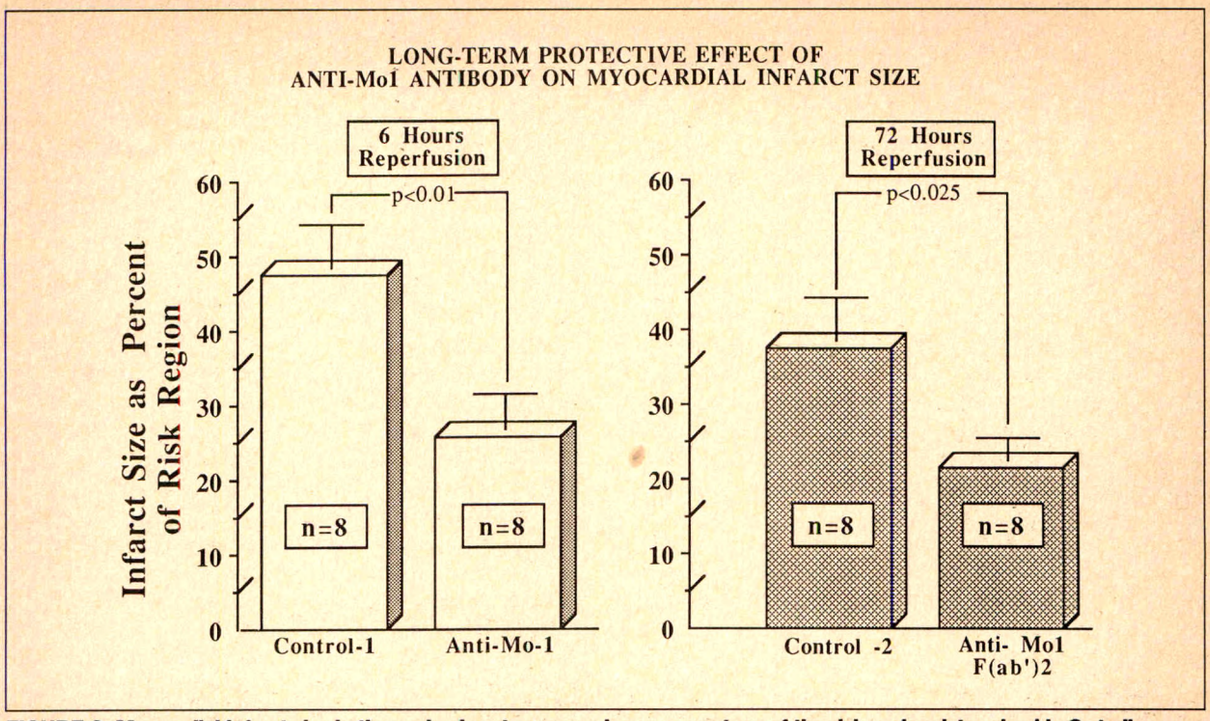


FIGURE 2. Myocardial infarct size in the canine heart expressed as a percentage of the risk region determined in 2 studies, each incorporating a control group and a group of animals treated with a murine monoclonal anti-Mo1 antibody. The graph on the *left* represents the results from a study in which coronary artery occlusion was maintained for 90 minutes followed by reperfusion for 6 hours, after which infarct size was determined. The treatment consisted of the administration of 1 mg/kg, intravenously, of Mo1 antibody given over 10 minutes, starting 45 minutes after occlusion of the left circumflex coronary artery. Inhibition of the Mo1 receptor by the anti-Mo1 antibody treatment resulted in a 46% reduction in myocardial infarct size compared with a placebo-treated group. To determine if the findings of the 6-hour study represented delay of infarction as opposed to prevention of irreversible injury, a second study was performed in which infarct size was determined 72 hours after reperfusion. The graph on the *right* represents data obtained in a study in which the F(ab'2) fragment of the Mo1 antibody was used in a dosing regimen of 1 mg/kg over 5 minutes, starting 45 minutes after coronary artery occlusion with repeated 0.5 mg/kg doses at 12, 24, 36 and 48 hours after reperfusion. Due to the relatively short half-life of the F(ab'2) fragment, repeated doses were necessary to modulate neutrophil function throughout the first 48 hours of the reperfusion period. Infarct size was determined 24 hours after the last dose of the Mo1 antibody (72 hours after reperfusion). Despite the withdrawal of the antibody treatment, infarct size was reduced when determined at 72 hours after reperfusion. The data suggested that a sustained reduction in infarct size can be achieved by the modulation of neutrophil reactivity.

IL-1 permitted each of the subunits to contribute to granulocyte adhesion.[42] Current data suggest that the α subunit of each of the 3 heterodimers contains a common region in the extracytoplasmic domain which mediates the interaction of the leukocyte with the endothelial cell or with the subendothelial structures during transmigration of leukocytes to regions of tissue injury and inflammation.[42]

The data demonstrate that inhibition of neutrophil adhesion reduced the extent of myocardial reperfusion injury and are in keeping with the proposition that neutrophils serve an important role as mediators of inflammation, extending myocardial injury beyond that caused by the ischemic process itself. The data also support the hypothesis that a significant number of myocardial cells at risk are viable after a 90-minute ischemic period, but then progress to an irreversible state of injury on reperfusion with the continued accumulation of PMNs. Studies from this laboratory[43] have identified a specific "time window" in which neutrophils participate in the extension of myocardial infarction after ischemia and reperfusion. The inhibition of neutrophil activation and accumulation in the myocardium over a prolonged period of time (>48 hours) is necessary to ensure a beneficial effect on the ultimate extension of irreversible myocardial injury. Interventions that have limited pharmacologic half-lives, while effective over brief periods of observation, may not show protective benefits if given in a single initial dose when infarct size is assessed at a period far removed from the point of administration of the treatment under study. Consideration must be given to the pharmacokinetic properties of selected interventions along with the dynamic and progressive nature of myocyte injury. The failure to consider the time course of events in myocardial ischemic and reperfusion injury may account for the discordant results in published reports. To date, published reports have failed to document a consistent progression of cellular injury attributable to the period of reperfusion and distinct from the progressive cell death entirely attributable to the period of ischemia.

NEUTROPHILS, OXYGEN RADICALS, MYOCARDIAL INJURY AND PROTECTION BY FREE RADICAL SCAVENGERS

Under some conditions of regional myocardial ischemia and reperfusion, neutrophils adhere to the vessel

wall at sites of inflammation and release toxic products capable of damaging the adjacent endothelium and myocytes within the reperfused region. It is recognized that neutrophils can release cytotoxic products extracellularly without undergoing destruction themselves. Neutrophils can release a variety of mediators capable of promoting tissue injury, including proteolytic enzymes, platelet-activating factor, arachidonic acid metabolites and activated species of oxygen. The last mentioned group of neutrophil-derived products, superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl anion (·OH) and hypochlorous anion (OCl-) are significant cytotoxic products derived from the metabolism of molecular oxygen on perturbation of the PMN. The generation of cytotoxic metabolites of oxygen, generated within the microenvironment formed between the adherent activated PMNs and altered endothelial cells, leads to an increase in vascular permeability and myocyte damage. This situation is "explosive" on reperfusion as neutrophils are directed and attracted to the reperfused region under the influence of the local accumulation of chemoattractants. During an extended period of regional ischemia of ≥40 minutes,[14] the stage is set for the neutrophil-mediated inflammatory response and injury that involves normal or reversibly injured cells and is accelerated by reperfusion of the ischemic region. Reperfusion injury, therefore, involves cells that were viable or recoverable up until the time that reperfusion was instituted. The extension of cell death, on reperfusion of the ischemic myocardium, is mediated by the neutrophil-derived cytotoxic products of oxygen metabolism. In the absence of reperfusion, all cells that are ischemic for a sufficiently long period will undergo irreversible changes, and reperfusion is essential for survival of the myocytes that are viable up until the time of reperfusion. However, a portion of the still viable myocardial cells will undergo further injury due to the cytotoxic actions of the reactive species of oxygen.

Jolly et al[44] were the first to provide evidence for the in vivo participation of oxygen radicals in myocardial reperfusion injury. They demonstrated that the administration of superoxide dismutase (SOD) plus catalase to anesthetized dogs, subjected to a 90-minute interval of regional myocardial ischemia followed by reperfusion, reduced ultimate infarct size when the scavenger enzymes were administered either before the induction of regional myocardial ischemia or 15 minutes before myocardial reperfusion. However, the enzymes were without beneficial effect if they were infused 40 minutes after reperfusion had been instituted. The data suggested that an extension of myocardial injury, in addition to that associated with the ischemia-induced myocardial cell death, occurred very early in reperfusion, and myocyte damage was attenuated by pretreatment with appropriate antioxidants. Subsequent studies have demonstrated that SOD, without the addition of catalase, was equally effective in preventing the extension of myocardial injury, thereby implicating superoxide anion as the primary mediator of the myocardial damage associated with reperfusion. The relatively short pharmacologic half-life (6 to 10 minutes) of SOD is a drawback to the study of the scavenger in experimental protocols that are extended several days after reperfusion. Neutrophil chemoattraction to the ischemically injured myocardium and the local formation of neutrophil-derived reactive species of oxygen will continue to effect a cytotoxic influence on the viable myocardial cells in the reperfused tissue. The free radical-induced injury is initiated on reperfusion and continues until mechanisms, still to be elucidated, bring about a cessation of the inflammatory response.

Disagreement regarding the cardioprotective role of SOD may relate to the use of different durations for induction of ischemic injury and reperfusion. To investigate this concept we undertook studies that used a modified form of SOD in which the enzyme was conjugated to polyethylene glycol (PEG-SOD).[45] The conjugated form of SOD has a pharmacologic half-life of 30 hours. Significant plasma SOD activity was demonstrated in the dog up to 7 days after a single intravenous administration of 1,000 U/kg of PEG-SOD. Two protocols, differing in the mode of administration and duration of the reperfusion interval, were used. Dogs were subjected to occlusion of the circumflex coronary artery for 90 minutes, then reperfused for either 6 hours (protocol A) or for 4 days (protocol B). The dogs received either PEG conjugated to albumin (PEG-ALB) or PEG-SOD, 1,000 U/kg. In protocol A, treatment was administered starting 15 minutes before coronary artery occlusion and continued for 2 hours, terminating 15 minutes after reperfusion. Infarct size was determined 6 hours later. In protocol B, the conjugated proteins were given 15 minutes before reperfusion and ended simultaneously with reperfusion. Infarct size was measured after 4 days. A significant reduction in myocardial infarct size, expressed as a percent of the area at risk, was observed in protocol A in the group of dogs that received PEG-SOD compared with the PEG-ALB–treated controls. Likewise, in the extended protocol, in which infarct size was determined 4 days after reperfusion, the PEG-SOD–treated group had a significant reduction in ultimate infarct size (Fig. 3). Hemodynamic variables did not differ during the period of coronary artery occlusion. The respective collateral blood flows to the inner two-thirds of ischemic myocardium, determined 60 minutes after occlusion, did not differ between the groups. Infarct size was inversely related to collateral blood flow in the PEG-ALB–treated group. The regression line describing the relationship between the extent of irreversible myocardial injury and collateral blood flow was shifted downward (analysis of covariance, $p = 0.01$) in the group of dogs treated with PEG-SOD. With use of the mean collateral blood flow to the inner two-thirds of the ischemic myocardium as a covariate, infarct size, expressed as a percentage of the area at risk, was smaller for the PEG-SOD–treated group than for the PEG-ALB–treated group ($p < 0.05$). The data demonstrated that PEG-SOD achieved a reduction in ultimate infarct size when quantitation of myocardial injury was performed after 4 days of reperfusion, a time when the plasma SOD activity was maintained well above that found in the PEG-ALB control group. These data are consistent with studies cited which demonstrated the necessity to suppress neutrophil function up to 48 hours to effect and maintain a reduction in infarct size determined

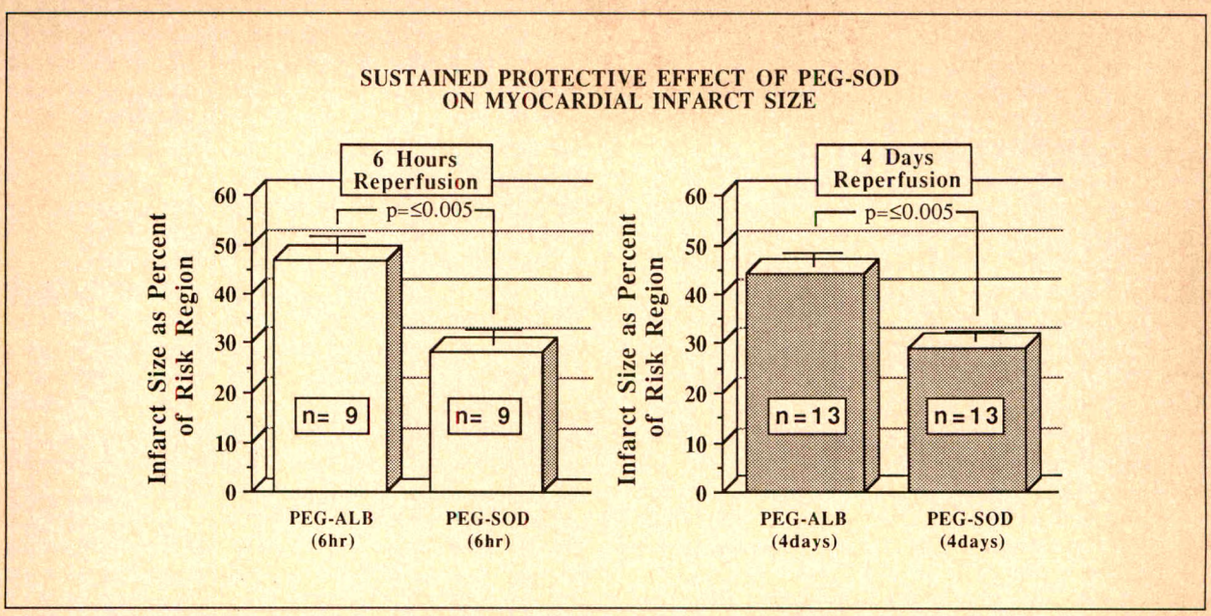


FIGURE 3. The effect of polyethylene-glycol conjugated superoxide dismutase (PEG-SOD) on myocardial infarct size due to a 90-minute occlusion and subsequent reperfusion of the left circumflex coronary artery in the canine heart. A single dose of PEG-SOD of 1,000 U/kg was administered before reperfusion in each of the 2 studies. The control groups received PEG conjugated to albumin (PEG-ALB) so that the administered amount of PEG and conjugated protein was comparable in all dogs. Infarct size in the 2 groups of dogs, depicted on the *left*, was determined after 6 hours of reperfusion. The 2 groups of dogs shown on the *right* had infarct measurements obtained 4 days after reperfusion. The data illustrated that the PEG-SOD with a 30-hour plasma half-life is able to provide sustained protection against the cytotoxic effects of superoxide anion derived in part from the infiltration of inflammatory cells into the reperfused myocardium.

at 72 hours.[43] These observations support the hypothesis that a critical "time window" exists during which antineutrophil or antioxidant therapy, or both, must be maintained to effect a reduction in the ultimate extent of the infarcted myocardium after periods of ischemia and reperfusion. PEG-SOD may have efficacy over that of the native enzyme because of its continued presence in the circulation and its ability to adhere to the surface of the vascular endothelium. PEG conjugation of SOD enhances cell association and uptake of the enzyme in a manner that renders the vascular endothelium more oxidant resistant.

The vulnerability of the endothelium to injury from reactive species of oxygen may be related to a number of factors, which include anatomic proximity to activated and invading inflammatory cells and localization of xanthine oxidase activity within endothelial cells. Vascular endothelial cells subjected to an ischemic equivalent of anoxic incubation followed by reoxygenation become effective generators of oxygen free radicals as determined by electron paramagnetic resonance measurements with a spin trap agent, 5,5-dimethyl-1-1-pyrroline-1-oxide.[46] SOD or catalase abolished the radical signal, suggesting that oxygen is sequentially reduced from O_2 to H_2O_2 to ·OH. Attenuation of the free radical signal by oxypurinol suggested that xanthine oxidase was a major source of the superoxide anion. It is conceivable that on reperfusion of the ischemic myocardium, the endothelial cells, as well as the adherent and infiltrating neutrophils, may provide the initial source of cytotoxic species of reduced oxygen and that the subsequent inflammatory process, involving the continued migration and accumulation of PMNs to the injured myocardium, provides a sustained source of oxygen radicals that diminish with time as reparative processes occur.

Interpretation of data based on inhibition of free radical production by pharmacologic inhibition of xanthine oxidase are cautioned. Recent data suggest that the rate of conversion of the dehydrogenase form of the enzyme to the oxidase form, in the rat heart, is too slow to account for the observed results.[47] It has been reported that allopurinol scavenges ·OH at rates comparable to those of mannitol.[48] Oxypurinol, the active metabolite of allopurinol, is more effective as a scavenger of ·OH. Time-dependent formation of the active metabolite in animals pretreated with allopurinol may explain the failure of some investigators[49] to observe a protection of the ischemic myocardium when the drug was evaluated acutely, as opposed to studies in which a pretreatment regimen was used permitting accumulation of the metabolite, oxypurinol, in which a reduction in ultimate infarct size was reported.[50,51] Furthermore, oxypurinol combines with the myeloperoxidase-derived oxidant, hypochlorous acid, preventing the latter from inactivating α_1-protease inhibitor and thereby protecting inflamed tissues from the damaging effects of elastase.[48]

OTHER FREE RADICAL SCAVENGERS IN THE PREVENTION OF MYOCARDIAL REPERFUSION INJURY

Previous studies have shown that sulfhydryl-containing compounds, including mercaptoproprioyl glycine (MPG), are capable of reacting with free radicals and inhibiting their biologic effects.[52,53] Mitsos et al[54] report-

ed the in vitro free radical-scavenging effects of MPG, as well as its potential to reduce myocardial infarct size in the canine heart subjected to 90 minutes of regional ischemia followed by 6 hours of reperfusion. The free radical scavenger was effective when administered intravenously just before the onset of reperfusion, suggesting that the sulfhydryl compound protects against that component of myocyte injury associated with reperfusion. Related observations regarding the cardioprotective effects of MPG have been provided by other investigators who have examined the phenomenon of myocardial stunning. It was noted that SOD, as well as MPG, were equally effective in restoring regional contractile function to the heart made ischemic for a brief period (15 minutes) followed by reperfusion.[55,56] The administration of the scavengers was effective when given before the onset of ischemia or immediately before reperfusion. If administration was delayed after the start of reperfusion, no benefit was demonstrated. These findings are reminiscent of the initial studies with SOD[4] in which salvage of myocardial tissue was accomplished only if the scavenger had been given before the onset of reperfusion.

The recognition that sulfhydryl-containing compounds could scavenge oxygen free radicals and provide a degree of protection against myocardial reperfusion injury and myocardial stunning led Westlin and Mullane[57] to explore the cardioprotective actions of other sulfhydryl-containing compounds. Several angiotensin-converting enzyme (ACE) inhibitors were examined for their ability to suppress superoxide anion formation in vitro and to improve postischemic cardiac function in vivo in a canine model of regional myocardial ischemia and reperfusion. Three sulfhydryl-containing ACE inhibitors, captopril, its stereoisomer SQ 14,534, and an analog, zofenopril (SQ 27,703) were compared with enalaprilat and teprotide. The latter 2 agents lack the sulfhydryl group, but inhibit ACE. Two additional sulfhydryl-containing compounds, MPG and N-acetylcysteine (NAC), which are not ACE inhibitors, were studied for suppression of free radical formation in vitro. The autooxidation of epinephrine to adrenochrome is mediated by superoxide anions and was inhibited by captopril, SQ 14,534, and zofenopril, with similar IC_{50} values of 8 to 10 μM, but not enalaprilat or teprotide (IC_{50} greater than 1,000 μM). The autooxidation reaction is inhibited as well by MPG and NAC. Captopril, MPG or NAC, but not teprotide or enalaprilat, were shown to scavenge superoxide anion production by the purine-xanthine oxidase reaction and by canine-activated neutrophils. Therefore, captopril scavenges superoxide anions in vitro independent of an action on ACE; an action that is most likely related to the presence of a sulfhydryl moiety. Pretreatment of dogs with captopril, intravenously (5 mg/kg), before occlusion of the coronary artery for 15 minutes followed by reperfusion resulted in a 40 to 60% return to active shortening within 60 minutes of reperfusion. However, equihypotensive doses of enalaprilat did not improve segmental function during reperfusion. Dogs given captopril immediately before restoring coronary blood flow had a similar return of function as that observed in dogs treated with the drug before occlusion. SQ 14,534, the isomer of captopril, which is 100-fold less potent as an ACE inhibitor, but equipotent in scavenging superoxide anions, also improved reperfusion-induced cardiac dysfunction when administered at reperfusion (5 mg/kg). Captopril improved postischemic contractile derangements by a mechanism independent of ACE inhibition. Restoration of blood supply to the ischemic myocardium provoked ventricular fibrillation in 37.5% of control dogs, but in only 9% of those administered enalaprilat and 0% of captopril-treated dogs. SQ 14,534 did not reduce the incidence of ventricular fibrillation (40%), indicating that the antifibrillatory actions may be related to ACE inhibition, or to a direct effect of the free radical scavenger on the integrity of the coronary vascular endothelium and the preservation of regional coronary artery blood flow.

CONCLUSIONS

Regardless of the cellular site of generation (endothelial cell, neutrophil or other cellular loci), the role of reactive species of oxygen in mediating cellular injury associated with reperfusion has gained wide support through a number of studies that have been reviewed recently.[58–61] These studies have not always been in agreement with the concept that reperfusion of the ischemic myocardium may result in an extension of injury beyond that which has resulted from the ischemic insult itself. We have concluded that the failure to obtain agreement among laboratories is related to differences in the models used with respect to the instrumentation of the heart in chronic animal studies, the duration of occlusion (40 vs 90 minutes), and the duration of reperfusion (6 hours vs 4 days).[43] The pharmacokinetic properties of interventions used to modify the extent of reperfusion injury must be given special consideration because the neutrophil-mediated component of reperfusion injury may be operative for several days.[46] Studies reporting negative effects with native SOD may be related to the short half-life of its free radical-scavenging capacity, which compromises the chances of observing a protective effect after 4 days of reperfusion.[45] This concern is applicable to other interventions studied in animal models in which assessment of efficacy is made several days after cessation of the treatment regimen. Because the PMN is implicated as being a major contributor to the observed injury on reperfusion, it is essential that the applied stimulus (ischemia) required for the ultimate chemoattraction of the PMN to the reperfused region be of sufficient duration. Short ischemic intervals (40 minutes), as opposed to longer (90 minutes) times of ischemic injury, may not serve as a sufficient stimulus for neutrophil recruitment,[14] thus making it unlikely that interventions designed to mitigate against the deleterious effects of neutrophil-dependent cytotoxic products will manifest their therapeutic effect.[62] The time-dependent relationship between the duration of regional myocardial ischemia and the manifestation of reperfusion injury has been suggested by the study of Eng et al[63] and must be taken into consideration in the design of an experimental protocol for the study of reperfusion injury and its modification by pharmacologic interventions. The ability of infarct expansion to develop late in the reperfusion period must

be recognized.[64,65] The modulation of the extent of reperfusion injury with an intervention possessing a relatively short pharmacologic half-life in relation to the period of reperfusion must be appreciated in the protocol design.[45]

REFERENCES

1. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death. I: myocardial infarct size vs. duration of coronary occlusion in dogs. *Circulation 1977;56:786–793.*

2. Topol EJ. Advances in thrombolytic therapy for acute myocardial infarction. *J Clin Pharmacol 1987;26:735–745.*

3. Hearse DJ, Humphrey SM, Nayler WG, Slade A, Border D. Ultrastructural damage associated with reoxygenation of the anoxic myocardium. *J Mol Cell Cardiol 1975;5:315–324.*

4. Jolly SR, Kane WJ, Bailie MB, Abrams GD, Lucchesi BR. Canine myocardial reperfusion injury: its reduction by the combined administration of superoxide dismutase and catalase. *Circ Res 1984;54:277–285.*

5. Romson JL, Hook BG, Kunkel SL, Abrams GD, Schork MA, Lucchesi BR. Reduction of the extent of ischemic myocardial injury by neutrophil depletion in the dog. *Circulation 1983;67:1016–1023.*

6. Mullane KM, Read N, Salmon JA, Moncada S. Role for leukocytes in acute myocardial infarction in anesthetized dogs: relationship to myocardial salvage by antiinflammatory drugs. *J Pharm Exp Ther 1984;228:510–552.*

7. Hess ML, Manson NH. Molecular oxygen: friend and foe. The role of the oxygen free radical system in the calcium paradox, and oxygen paradox and ischemia/reperfusion injury. *J Mol Cell Cardiol 1984;16:969–985.*

8. McCord JM. Oxygen-derived free radicals in post ischemic tissue injury. *N Engl J Med 1985;312:159–163.*

9. Lucchesi BR, Mullane KM. Leukocytes and ischemia-induced myocardial injury. *Ann Rev Pharmacol Toxicol 1986;26:201–224.*

10. Werns SW, Lucchesi BR. Leukocytes, oxygen radicals and myocardial injury due to ischemia and reperfusion. *Free Radicals Biol Med 1988;4:31–37.*

11. Bevilacqua MO, Poker JS, Mendrick DL, Cotran RS, Gimbrone MA Jr. Identification of an inducible endothelial leukocyte adhesion molecule, ELAM-1. *Proc Natl Acad Sci 1987;84:9238–9242.*

12. Sommers HM, Jennings RB. Experimental acute myocardial infarction: histologic and histochemical studies of early myocardial infarcts induced by temporary or permanent occlusion of a coronary artery. *Lab Invest 1964;13:1491–1503.*

13. Engler RL, Dahgren MD, Peterson MA, Dobbs A, Schmid-Schonbein GW. Accumulation of polymorphonuclear leukocytes during 3-h experimental ischemia. *Am J Physiol 1986;251:H93–H100.*

14. Go LO, Murry CE, Richard VJ, Weischedel GR, Jennings RB, Reimer KA. Myocardial neutrophil accumulation during reperfusion and reversible or irreversible ischemic injury. *Am J Physiol 1988;255:H1188–H1198.*

15. Jennings RB, Reimer KA. Factors involved in salvaging ischemic myocardium: effect of reperfusion of arterial blood. *Circulation 1984;68:suppl 1:125–136.*

16. Werns SW, Lucchesi BR. Myocardial ischemia and reperfusion: the role of oxygen radicals in tissue injury. *Cardiovasc Drugs Ther 1989;2:761–769.*

17. Hill JH, Ward PA. The phlogistic role of C3 leukotactic fragments in myocardial infarcts of rats. *J Exp Med 1975;133:885–900.*

18. Jugdutt BI, Hutchins GM, Bulkley BH, Pitt B, Becker LC. Effect of indomethacin on collateral blood flow and infarct size in the conscious dog. *Circulation 1979;59:734–743.*

19. Flynn PJ, Becker WK, Vercellotti GM, Weisdorf DJ, Craddock PR, Hammerschmidt DE, Lillehei RC, Jacolb H. Ibuprofen inhibits granulocyte responses to inflammatory mediators. *Inflammation 1984;8:33–44.*

20. Jugdutt BI, Hutchin GM, Bulkley BH, Becker LC. Salvage of ischemic myocardium by ibuprofen during infarction in the conscious dog. *Am J Cardiol 1980;46:74–82.*

21. Romson JL, Hook BG, Rigot VH, Schork MA, Swanson DP, Lucchesi BR. The effect of ibuprofen on accumulation of indium-111-labeled platelets and leukocytes in experimental myocardial infarction. *Circulation 1982;666:1002–1011.*

22. Simpson PJ, Mitsos SE, Ventura A, Gallagher KP, Fantone JC, Abrams GC, Schork MA, Lucchesi BR. Prostacyclin protects ischemic-reperfused myocardium in the dog by inhibition of neutrophil activation. *Am Heart J 1987;113:129–137.*

23. Simpson PJ, Mickelson JK, Fantone JC, Gallagher KP, Lucchesi BR. Iloprost inhibits neutrophil function in vitro and limits experimental infarct size in canine heart. *Circ Res 1987;60:666–673.*

24. Simpson PJ, Mickelson J, Fantone JC, Gallagher KP, Lucchesi BR. Reduction of experimental canine myocardial infarct size with prostaglandin E_1: inhibition of neutrophil migration and activation. *J Pharm Exp Ther 1988;244:619–624.*

25. Hill JH, Ward PA. The phlogistic role of C3 leukotactic fragments in myocardial infarcts of rats. *J Exp Med 1975;133:885–900.*

26. Hill JH Ward PA. C3 leukotactic factors produced by a tissue protease. *J Exp Med 1969;130:505–518.*

27. Rossen RD, Michael LH, Kagiyama A, Savage HE, Hanson G, Reisberg MA, Moake JN, Kim SH, Self D, Giannini E, Entman ML. Mechanism of complement activation after coronary artery occlusion. Evidence that myocardial ischemia in dogs causes release of constituents of myocardial subcellular origin that complex with human C1q in vivo. *Circ Res 1988;62:572–584.*

28. Crawford MH, Grover FL, Kolb WP, McMahan A, O'Rourke RA, McManus LM, Pinckard RN. Complement and neutrophil activation in the pathogenesis of ischemic myocardial injury. *Circulation 1988;78:1449–1458.*

29. Muller-Eberhard HJ. Complement: chemistry and pathways. In: Gallin JI, Goldstein R, Synderman R, eds. Inflammation: Basic Principles and Clinical Correlates. *New York: Raven Press, 1988:21–53.*

30. Strieter RM, Kunkel SL, Showel HJ, Marks RM. Monokine induced gene expression of a human endothelial cell-derived neutrophil chemotactic factor. *Biochem Biophys Res Comm 1988;156:1340–1345.*

31. Thelen M, Peveri P, Kernen P, Tscharner VV, Walz A, Baggiolini M. Mechanism of neutrophil activation by NAF, a novel monocyte-derived peptide agonist. *FASEB J 1988;2:2702–2706.*

32. Smith CW, Rothlein R, Hughes BJ, Mariscalco MM, Rudloff HE, Schmalstic FC, Anderson DC. Recognition of an endothelial determinant for CD-18 dependent human neutrophil adherence and transendothelial migration. *J Clin Invest 1988;82:1746–1756.*

33. Prober JS. Cytokine-mediated activation of vascular endothelium. Physiology and pathology. *Am J Pathol 1988;133:426–433.*

34. Bevilacqua MO, Poker JS, Mendrick DL, Cotran RS, Gimbrone MA Jr. Identification of an inducible endothelial leukocyte adhesion molecule, ELAM-1. *Proc Natl Acad Sci 1987;84:9238–9242.*

35. Ismail G, Morganroth ML, Todd RF III, Boxer LA. Prevention of pulmonary injury in isolated perfused rat lungs by activated human neutrophils preincubated with anti-Mo1 monoclonal antibody. *Blood 1987;69:1167–1174.*

36. Anfors K, Lundberg C, Lindbom L, Lunderg K, Beaty PG, Harlan JM. A monoclonal antibody to membrane glycoprotein complex CD18 inhibits polymorphonuclear leukocyte accumulation and plasma leakage in vivo. *Blood 1987;69:338–340.*

37. Simpson PJ, Todd RF III, Fantone JC, Mickelson JK, Griffin JD, Lucchesi BR. Reduction of experimental canine myocardial reperfusion injury by a monoclonal antibody (anti-Mo1, Anti-CD11b) that inhibits leukocyte adhesion. *J Clin Invest 1988;81:624–629.*

38. Simpson PJ, Todd RF, Mickelson JK, Fantone JC, Gallagher KP, Tamura Y, Lee KA, Kitzen JM, Lucchesi BR. Sustained limitation of myocardial reperfusion injury by a monoclonal antibody that inhibits leukocyte adhesion. *Fed Proc 1988;2:A1237.*

39. Mullane KM, Read N, Salmon JA, Moncada S. Role for leukocytes in acute myocardial infarction in anesthetized dogs: relationship to myocardial salvage by antiinflammatory drugs. *J Pharm Exp Ther 1984;228:510–552.*

40. Flynn PJ, Becker WK, Vercellotti GM, Weisdorf DJ, Craddock PR, Hammerschmidt DE, Lillehei RC, Jacolb H. Ibuprofen inhibits granulocyte responses to inflammatory mediators. *Inflammation 1984;8:33–44.*

41. Romson JL, Hook BG, Rigot VH, Schork MA, Swanson DP, Lucchesi BR. The effect of ibuprofen on accumulation of indium-111-labeled platelets and leukocytes in experimental myocardial infarction. *Circulation 1982;66:1002–1011.*

42. Arnaout MA, Lanier LL, Faller DV. Relative contribution of the leukocyte molecules Mo1, LFA-1, and p150,95 (leuM5) in adhesion of granulocytes and monocytes to vascular endothelium is tissue-and stimulus specific. *J Cell Physiol 1988;137:305–309.*

43. Simpson PJ, Fantone JC, Mickelson JK, Gallagher KP, Lucchesi BR. Identification of a time window for therapy to reduce experimental canine myocardial injury: suppression of neutrophil activation during 72 hours of reperfusion. *Circ Res 1988;63:1070–1079.*

44. Jolly SR, Kane WJ, Bailie MB, Abrams GD, Lucchesi BR. Canine myocardial reperfusion injury: its reduction by the combined administration of superoxide dismutase and catalase. *Circ Res 1984;54:277–285.*

45. Tamura Y, Chi I, Driscoll E, Jr, Hoff PT, Freeman BA, Gallagher KP, Lucchesi BR. Superoxide dismutase conjugated to polyethylene glycol provides sustained protection against myocardial ischemia/reperfusion injury in canine heart. *Circ Res 1988;63:944–959.*

46. Zweier JL, Kuppusamy P, Lutty GA. Measurement of endothelial cell free radical generation: evidence for a central mechanism of free radical injury in postischemic tissues. *Proc Natl Acad Sci USA 1988;85:4046–4050.*

47. Engerson TD, McKelvev TG, Jones HP. Xanthine dehydrogenase to xanthine oxidase conversion in ischemic rat tissues. *Fed Proc 1989;3:A628.*

48. Hoey BM, Butler J, Halliwell B. On the specificity of allopurinol and oxypurinol as inhibitors of xanthine oxidase. A pulse radiolysis determination of rate constants for reaction of allopurinol and oxypurinol with hydroxyl radicals. *Free Rad Res Comms 1988;4:259–263.*

49. Reimer KA, Jennings RB. Failure of the xanthine oxidase inhibitor allopurinol to limit infarct size after ischemia and reperfusion in dogs. *Circulation 1985;71:1069–1075.*

50. Werns SW, Shea MJ, Mitsos SE, Dysko RC, Fantone JC, Schork MA, Abrams GD, Pitt B, Lucchesi BR. Reduction of the size of infarction by allopurinol in the ischemic-reperfused canine heart. *Circulation 1986;73:518–524.*

51. Werns SW, Grum CM, Ventura A, Lucchesi BR. Effects of allopurinol or oxypurinol on myocardial reperfusion injury. *Circulation 1987;76:IV-97.*

52. Betts WH, Cleland LG, Gee DJ, Whitehouse MW. Effects of D-penicillamine on a model of oxygen-derived free radical mediated tissue damage. *Agents and Actions 1984;283–290.*
53. Devi P. Chemical radiation protection by alpha-mercaptopropionyl glycine. *J Nucl Med Allied Sci 1983;27:327–336.*
54. Mitsos SE, Fantone JC, Gallagher KP, Walden KM, Simpson PJ, Abrams GD, Schork MA, Lucchesi BR. Canine myocardial reperfusion injury: protection by a free radical scavenger, N-2-mercaptopropionyl glycine. *J Cardiovas Pharmacol 1986;8:978–988.*
55. Myers ML, Bolli R, Lekich RF, Hartley CJ, Roberts R. Enhancement of recovery of myocardial function by oxygen free-radical scavengers after reversible regional ischemia. *Circulation 1985;72:915–921.*
56. Myers ML, Bolli R, Lekich RF, Hartley CJ, Roberts R. N-2-mercaptopropionylglycine improves recovery of myocardial function following reversible regional ischemia. *JACC 1986;8:1161–1168.*
57. Westlin W, Mullane K. Does captopril attenuate reperfusion-induced myocardial dysfunction by scavenging free radical? *Circulation 1988;77:suppl I:I-30–I-39.*
58. McCord JM. Oxygen-derived free radicals in post ischemic tissue injury. *N Engl J Med 1985;312:159–163.*
59. Lucchesi BR, Mullane KM. Leukocytes and ischemia-induced myocardial injury. *Ann Rev Pharmacol Toxicol 1986;26:201–224.*
60. Werns SW, Lucchesi BR. Leukocytes, oxygen radicals and myocardial injury due to ischemia and reperfusion. *Free Radicals Biol Med 1988;4:31–37.*
61. Southorn PA, Powis G. Free radicals in medicine: II. Involvement in human disease. *Mayo Clinic Proc 1988;63:390–408.*
62. Uraizee A, Reimer KA, Murry CE, Jennings RB. Failure of superoxide dismutase to limit myocardial infarct size in a 40 minutes ischemia/four days reperfusion model in dogs. *Circulation 1987;75:1237–1248.*
63. Eng C, Cho S, Factor SM, Kirk ES. A nonflow basis for the vulnerability of the subendocardium. *JACC 1987;9:374–379.*
64. Brown EJ Jr, Mannisi JA, Lillis OI, Cohn PF. Time course of reperfusion induced reversal of early myocardial expansion. *JACC 1989;13:109A.*
65. Murry CE, Richard VJ, Jennings RB, Reimer KA. Prolonged reperfusion attenuates the protective effect of preconditioning myocardium with a brief episode of ischemia. *Fed Proc 1989;3:A629.*

Captopril and Enalaprilat Do Not Scavenge the Superoxide Anion

Rakesh C. Kukreja, PhD, Hermes A. Kontos, MD, PhD, and Michael L. Hess, MD

The ability of captopril and enalaprilat, 2 angiotensin-converting enzyme (ACE) inhibitors, to scavenge superoxide anion radical was examined. With use of a number of superoxide-generating systems, such as xanthine-xanthine oxidase, phorbol myristate acetate-activated neutrophils, auto-oxidizing dihydroxyfumarate, and auto-oxidation of epinephrine to adrenochrome, captopril was seen not to scavenge superoxide directly, because it did not inhibit superoxide-dependent cytochrome c or nitroblue tetrazolium reduction. Superoxide-dependent cytochrome c reduction was inhibited only when captopril was preincubated with a lower concentration of cytochrome c (22 μM). This effect was due to a decrease in the concentration of cytochrome c, because captopril reduced cytochrome c directly. When this effect was compensated for, no cytochrome c reduction induced by superoxide was observed. Captopril inhibited the auto-oxidation of epinephrine to adrenochrome at pH 10.2 where this auto-oxidation is superoxide-dependent, and at pH 7.8 where it is superoxide-independent and superoxide dismutase insensitive. It appears that captopril, in this respect, acted as a nonspecific antioxidant, probably by reducing an intermediate in the complex oxidation of epinephrine to adrenochrome. Therefore, caution may be used in interpreting the role of captopril in the attenuation of reperfusion-induced myocardial dysfunction and in attributing this effect to the inhibition of free radical mechanism.

(Am J Cardiol 1990;65:24 I–27 I)

Captopril, an angiotensin-converting enzyme (ACE) inhibitor,[1] has a number of effects independent of ACE inhibition; these include an anti-inflammatory action,[2,3] cardioprotective effect against reperfusion-induced arrhythmias,[4] and attenuation of reperfusion-induced depression of myocardial function.[5] Recently, Westlin and Mullane[5] provided a possible explanation for these actions. These investigators found that captopril diminished the reduction of cytochrome c induced by superoxide generated by xanthine oxidase plus xanthine or by activated neutrophils, and that it also decreased the rate of auto-oxidation of epinephrine. They asserted that captopril scavenged superoxide and acted like superoxide dismutase (SOD). However, captopril contains a sulfhydryl group (SH) and, therefore, acts as a reducing agent. It is possible that because of this action, it may interfere with the cytochrome c reduction assay of superoxide. It is not clear from Westline and Mullane[5] whether this effect of captopril was taken into consideration. A reexamination of the superoxide scavenging capabilities of captopril, therefore, appeared in order. We also compared the superoxide scavenging capabilities of another ACE inhibitor, enalaprilat, the deesterified form of enalapril.

METHODS

We studied the ability of captopril and enalaprilat to scavenge superoxide in a variety of superoxide-generating systems described in the ensuing paragraph. In some experiments, the effects of dimethyl sulfoxide (DMSO [from Sigma]), a known hydroxyl radical scavenger, and of cysteine (Sigma), an SH-containing compound that is known not to scavenge superoxide directly were comparatively studied.

Xanthine-xanthine oxidase: Superoxide generated by xanthine oxidase action on xanthine was determined by monitoring cytochrome c reduction at 550 nm. A typical assay consisted of 50 μM xanthine (sodium salt, Sigma), 0.005 μ/ml xanthine oxidase (Boehringer Mannheim 20 μ/ml), 0.05 mM cytochrome c (Sigma) in potassium phosphate buffer (0.05 M, pH 7.8 at 22°C) containing 0.1 mM ethylenediaminotetra-acetate (EDTA). Captopril, enalaprilat or SOD were added in the reaction mixture before initiation of the reaction by xanthine oxidase. In some experiments, different concentrations of xanthine, cytochrome c or xanthine oxidase were used.

Phorbol myristate acetate–stimulated human neutrophils: Heparinized human blood was mixed with equal volumes of 2% dextran in 0.9% saline solution and the erythrocytes were allowed to settle for 1.5 to 2 hours at room temperature. The neutrophil-rich plasma was cen-

From the Division of Cardiology, Department of Medicine, Medical College of Virginia, Richmond, Virginia. This work was supported in part by Grants HL 40111 and HL 24917 from the National Institutes of Health, Bethesda, Maryland, and grant-in-aid 87061 from the American Heart Association, Dallas, Texas.

Address for reprints: Michael L. Hess, MD, Box 281, Cardiology Division, Medical College of Virginia, Richmond, Virginia 23298.

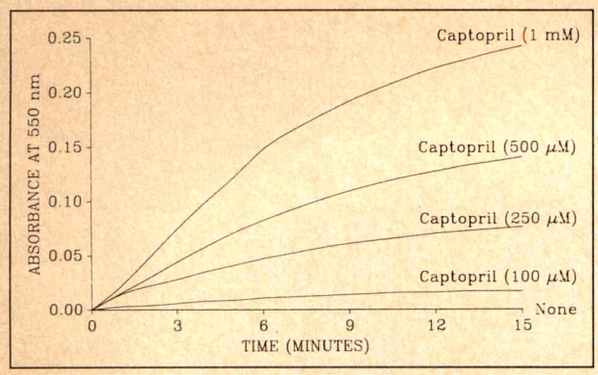


FIGURE 1. Dose-dependent reduction of cytochrome c by captopril. Captopril initiated immediate reduction of cytochrome c at 550 nm without the generation of superoxide by xanthine oxidase action on xanthine.

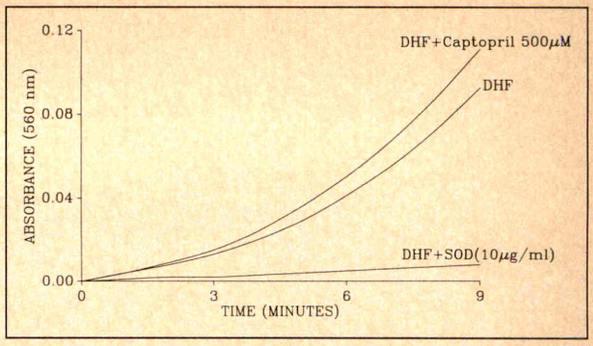


FIGURE 3. Superoxide generation from auto-oxidizing dihydroxyfumarate (DHF) and effects of captopril and superoxide dismutase (SOD). Captopril (500 μM) did not depress the superoxide-dependent nitroblue tetrazolium reduction at 560 nm, whereas SOD (10 μg/ml) did inhibit.

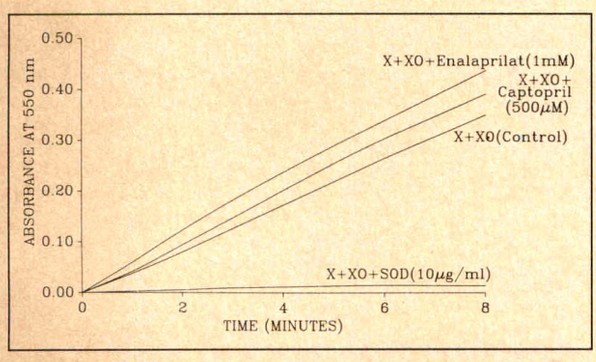


FIGURE 2. Inability of captopril to scavenge superoxide generated from xanthine oxidase (XO) action on xanthine. Captopril (500 μM) or enalapril (1 mM) were without any inhibitory effect on superoxide-dependent cytochrome c at 550 nm reduction, whereas superoxide dismutase (SOD) (10 μg/ml) inhibited rate of cytochrome c reduction under similar conditions.

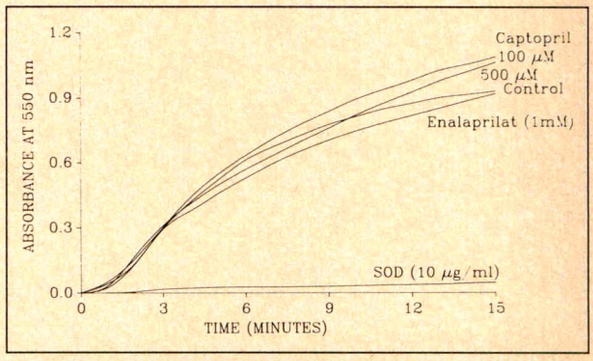


FIGURE 4. Inability of captopril or enalaprilat to inhibit superoxide-dependent cytochrome c reduction from phorbol myristate acetate–stimulated neutrophils. Superoxide dismutase (SOD) (10 μg/ml) but not captopril or enalaprilat inhibited superoxide-dependent cytochrome c reduction.

trifuged at 170 × g for 15 minutes. Contaminating erythrocytes were removed by hypotonic lysis and the neutrophils were washed with 0.9% saline solution before layering onto Ficoll-Hypaque density gradient and centrifuged at 170 × g for 20 minutes. The pellet was resuspended in Hank's buffer containing glucose, calcium and magnesium.

A typical assay consisted of 100 μM cytochrome c and 0.5×10^6 cells/ml in Hank's balanced salt solution. The cells were activated by phorbol myristate acetate in DMSO (200 ng/ml) and the rate of cytochrome c reduction was monitored at 550 nm for 10 to 15 minutes.

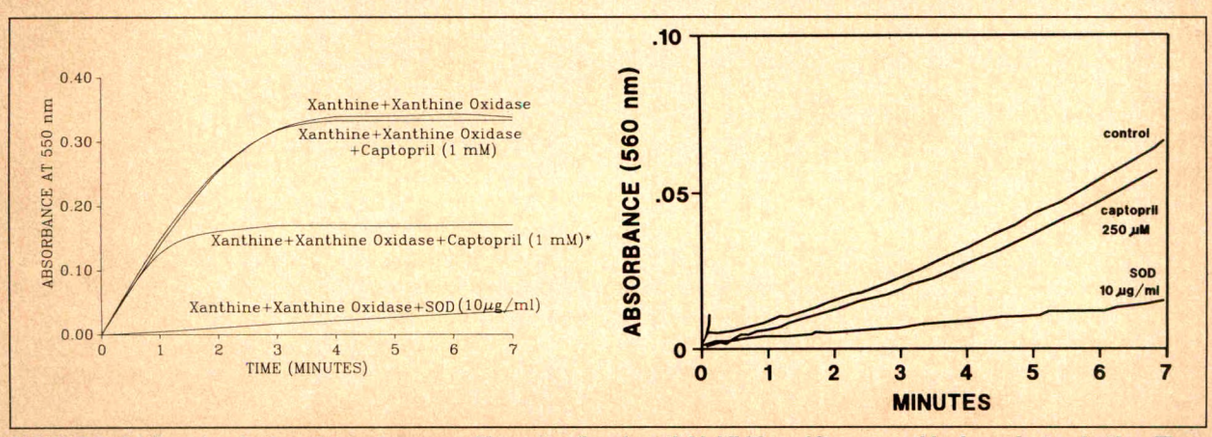


FIGURE 5. *Left,* preincubation of cytochrome c with captopril and partial inhibition of its superoxide-dependent reduction. The reaction mixture contained lower cytochrome c (22 μM), 0.02 U/ml xanthine oxidase and 152 μM xanthine. *Asterisk,* rate of cytochrome c reduction after preincubation with 1 mM cytochrome c for 30 minutes. *Right,* inability of captopril to inhibit superoxide-dependent nitroblue tetrazolium reduction under similar conditions. SOD = superoxide dismutase.

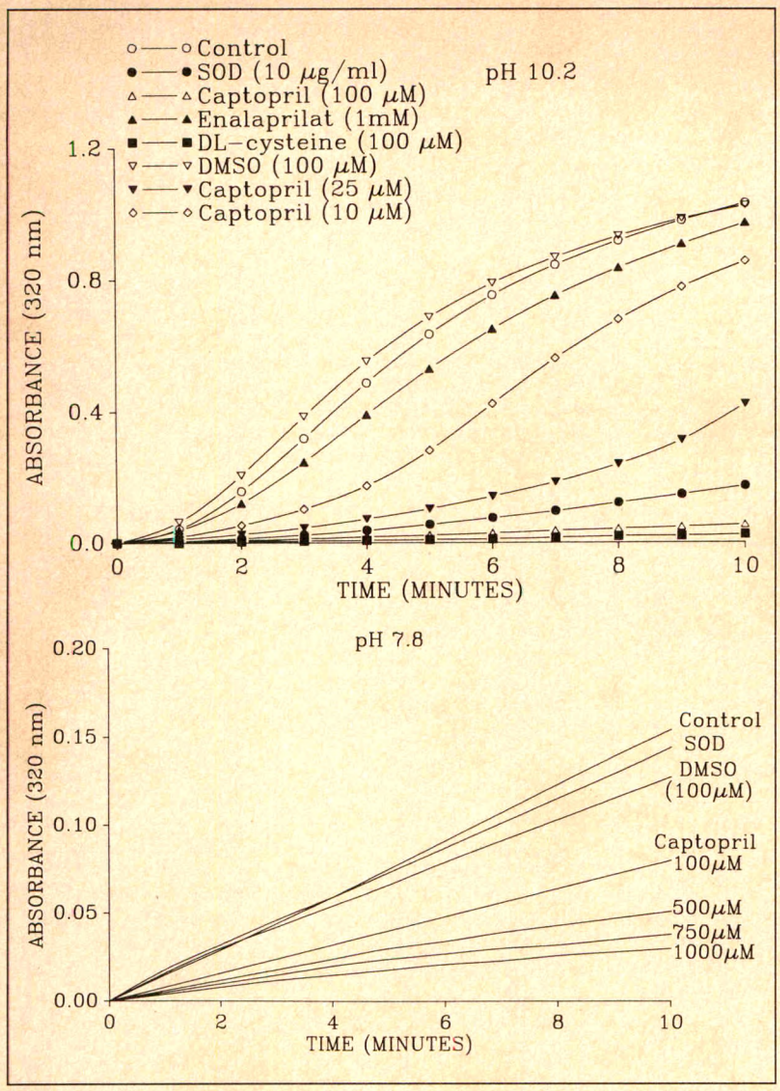


FIGURE 6. ***Top,*** **time course of epinephrine oxidation at pH 10.2 and effect of captopril, superoxide dismutase (SOD), enalaprilat, cysteine and dimethyl sulfoxide (DMSO). Captopril at 100 and 500 μM concentrations, cysteine (100 μM) and SOD (10 μg/ml) inhibited epinephrine oxidation. Enalaprilat (1 mM) or DMSO were without any effect. The rate of epinephrine oxidation was monitored at 320 nm.** ***Bottom,*** **time course of epinephrine oxidation at pH 7.8 and effects of SOD, captopril and DMSO. SOD (10 μg/ml) and DMSO (100 μM) were without any depressive effect on epinephrine oxidation at this pH, whereas captopril continued to inhibit in a dose-dependent manner from 100 to 1,000 μM. DL = racemic mixture of D- and L-isomers of cysteine.**

Captopril, enalaprilat or SOD were added before activation of cells by phorbol myristate acetate.

Auto-oxidation of dihydroxyfumarate: Superoxide generated during the auto-oxidation of dihydroxyfumarate was measured by nitroblue tetrazolium (NBT) reduction assay.[8] The standard assay mixture had a total volume of 3 ml and contained 50 μM NBT, 3.33 mM dihydroxyfumarate in 0.05M phosphate buffer containing 0.1 mM EDTA (pH 7.8). The rate of NBT reduction was monitored spectrophotometrically at 560 nm. Captopril or SOD were included in the reaction mixture to study their effects.

Epinephrine auto-oxidation: The auto-oxidation of epinephrine to adrenochrome was quantitated in vitro according to the method of Misra and Fridovich[7] and subsequently modified by Sun and Zigman.[6] Briefly, 10 μl of stock epinephrine (10^{-2} M) was used to initiate the reaction in buffer (0.1 M EDTA/50 mM sodium carbonate buffer, pH 10.2) in the presence or absence of captopril, enalaprilat or SOD. The rate of epinephrine oxidation was monitored at 320 nm up to 10 minutes. Epinephrine oxidation monitored at this wavelength was found to be more sensitive and gave more consistent results than that measured at 480 nm. The effect of SOD and captopril on the oxidation of epinephrine at 2 different pHs (7.8 and 10.2) was studied in potassium phosphate, or sodium carbonate buffers (0.05 M) containing 0.1 M EDTA. The pH 7.8 buffer contained 8.8×10^{-5} M ferrous sulfate as catalyst.[8]

RESULTS

Captopril reduced cytochrome c directly in a dose-dependent fashion (Fig. 1). Cysteine had the same effect, whereas enalaprilat had no such effect, showing that the reduction of cytochrome c induced by captopril was probably due to the presence of the SH group.

In contradiction to the results reported by Westlin and Mullane,[5] we found that captopril had absolutely no superoxide-scavenging capability. This was the case when superoxide was generated by xanthine plus xanthine oxidase (Fig. 2), by auto-oxidizing dihydroxyfumarate (Fig. 3), or by phorbol myristate acetate--activated neutro-

phils (Fig. 4). Because captopril reduced cytochrome c directly (Fig. 1), the resultant reduction in cytochrome c concentration is certain to result in a decreased rate of reduction under specific assay conditions such as lower cytochrome c concentration, higher xanthine oxidase and increased preincubation time with captopril. Fig. 5 (left) represents such a partial inhibition of cytochrome c when captopril (1 mM) was preincubated for 30 minutes before initiating reaction with xanthine oxidase. The diminution in the rate of reduction of cytochrome c, induced under these circumstances, was eliminated by adding additional cytochrome c to the reaction mixture. Under similar conditions, if NBT was used, which was not reduced directly by captopril, instead of cytochrome c, no detectable effect of captopril on the rate of reduction of this dye could be detected (Fig. 5, right). Clearly, the findings showed that captopril did not scavenge superoxide. The effect of cysteine was similar to that of captopril in all respects. When captopril was added to the reaction mixture immediately before the initiation of superoxide generation, no significant decrease in the rate of superoxide-induced reduction of cytochrome c was observed (Fig. 2 and 5, left).

Captopril and cysteine, but not enalaprilat, diminished the rate of auto-oxidation of epinephrine at pH 10.2; SOD had a similar inhibitory effect at this pH. The findings with captopril confirm the results of Westlin and Mullane.[5] Misra and Fridovich[7] showed that the auto-oxidation of epinephrine is a complex process, which can proceed by at least 2 independent pathways. At high pH (10.2), the auto-oxidation of epinephrine to adrenochrome is superoxide-dependent and, therefore, inhibited by SOD (Fig. 6, top). However, at lower pH (7.8), the auto-oxidation of epinephrine to adrenochrome is metal-catalyzed, and is independent of superoxide. For this reason we tested the effect of captopril on the auto-oxidation of epinephrine at the lower pH. Captopril, but not SOD or DMSO, inhibited the rate of oxidation of epinephrine (Fig. 6, bottom).

DISCUSSION

Our findings clearly show that captopril does not scavenge superoxide directly. The earlier suggestion by Westlin and Mullane[5] that captopril is a scavenger of superoxide is probably due to erroneous interpretation of the assays for superoxide used. Captopril, by virtue of its SH group, acts as a reducing agent and reduces cytochrome c, thereby reducing the concentration of this indicator in the assay of superoxide. This effect is dependent on the concentrations of xanthine oxidase, cytochrome c, captopril and the duration of preincubation used in this assay (Fig. 5, left). Westlin and Mullane[5] did not take into account the effect of this interaction of captopril with cytochrome c and misinterpreted the resultant decrease in the rate of superoxide-induced reduction of cytochrome c as due to scavenging of superoxide by captopril.

Our findings show that at pH 10.2 captopril reduced the rate of auto-oxidation of epinephrine to adrenochrome, a finding similar to that of Westlin and Mullane.[5] These investigators, however, interpreted this as indicating that captopril scavenges superoxide. Further analysis of the effects of captopril on the auto-oxidation of epinephrine shows that this interpretation is not warranted. Captopril interfered with the auto-oxidation of epinephrine at a lower pH where the auto-oxidation of epinephrine is independent of superoxide and where SOD has no effect.[7] A more reasonable interpretation, which is consistent with all of the findings, is that captopril, by virtue of its SH group, acts as a nonspecific antioxidant. Because DMSO was ineffective in inhibiting the auto-oxidation of epinephrine at pH 7.8, hydroxyl radical is probably not involved. The effect of captopril is probably exerted via reduction of an intermediate product in the complex of auto-oxidation of epinephrine to adrenochrome.

Whether this antioxidant effect of captopril is of clinical value cannot be evaluated from our experiments and has to be tested by direct experimentation in various situations in which oxidant injury to tissues occurs. In this respect, however, at least with regard to the antioxidant effects of captopril in the auto-oxidation of epinephrine, it is not superior to cysteine.

REFERENCES

1. Ondetti MA, Rubin B, Cushman DW. Design of specific inhibitors of angiotensin-converting enzyme: a new class of orally active antihypertensive agents. *Science 1977;196:441–444.*

2. Fantone JC, Schrier D, Weingarten B. Inhibition of vascular permeability changes in rats by captopril. *J Clin Invest 1982;69:1207–1211.*

3. Martin MFR, McKenna F, Bird HA, Surrall EK, Dixon JS, Wright V. Captopril: a new treatment for rheumatoid arthritis? *Lancet 1984;1:1325–1327.*

4. Woodward B, Zakaria M. Effect of some free radical scavengers on reperfusion-induced arrhythmias in the isolate rat heart. *J Mol Cell Cardiol 1985; 17:485–493.*

5. Westlin W, Mullane K. Does captopril attenuate reperfusion induced myocardial dysfunction by scavenging free radicals? *Circulation 1988;77:suppl I:I-130–I-139.*

6. Sun M, Zigman S. An improved spectrophotometric assay for superoxide dismutase based on epinephrine autoxidation. *Anal Biochem 1978;90:81–89.*

7. Misra HP, Fridovich I. The role of superoxide anion in the autoxidation of epinephrine and a simple assay for superoxide dismutase. *J Biol Chem 1972; 247:3170–3175.*

8. Kukreja RC, Okabe E, Schrier GM, Hess ML. Oxygen radical mediated lipid peroxidation and inhibition of Ca^{2+}-ATPase activity of cardiac sarcoplasmic reticulum. *Arch Biochem Biophys 1988;261:447–457.*

Neuroendocrine Activation After Acute Myocardial Infarction

Jay N. Cohn, MD

Neuroendocrine response after acute myocardial infarction (MI) results in activation of the sympathetic nervous system, the renin-angiotensin system, and vasopressin and atrial natriuretic peptide release. The net effect of this response is vasoconstriction, cardiac stimulation and regional flow redistribution that may have a favorable effect in some situations and a deleterious effect in others.

The possible adverse effects of vasoconstriction were studied in a Veterans Administration Cooperative Study that evaluated a 48-hour infusion of sodium nitroprusside in the setting of acute MI. In the presence of mild, probably primarily diastolic left ventricular dysfunction, nitroprusside appeared to have an adverse effect on long-term survival. However, in the presence of more severe, probably predominantly systolic dysfunction, nitroprusside had a favorable effect on the prognosis. Therefore, the decision of whether to accept or inhibit neuroendocrine activation in acute MI probably depends on the severity of the disease and the timing of the therapeutic intervals.

(Am J Cardiol 1990;65:28 I–31 I)

From the Department of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota. This study was supported in part by the Cooperative Studies Program, Veterans Administration, Minneapolis, Minnesota.

Address for reprints: Jay N. Cohn, MD, Box 488, University of Minnesota Medical School, Minneapolis, Minnesota 55455.

The circulatory disturbance of acute myocardial infarction (MI) usually is accompanied by neuroendocrine stimulation. Therapy used in the treatment of acute MI may contribute to the neurohormonal response. The purpose of this study was to examine the physiologic implications of the neurohormonal response and to determine if the net effect of this response is favorable or unfavorable.

EVIDENCE FOR NEUROENDOCRINE STIMULATION

Plasma catecholamines increase in patients with acute MI.[1–3] Some of the increase in circulating norepinephrine may be the result of a reduction in norepinephrine clearance. It is also likely that increased levels of circulating norepinephrine reflect an increase in spillover of norepinephrine from the synaptic cleft into the bloodstream.[4] The regional source of the norepinephrine in the acute MI syndrome is unknown. Because infarcted myocardium rapidly becomes depleted of norepinephrine,[5] it is interesting to speculate a myocardial source of the high circulating levels of norepinephrine. However, the magnitude of the norepinephrine response indicates that it is from a generalized sympathetic reflex response distributed throughout the sympathetic nervous system.

Because the magnitude of the sympathetic response in patients with acute MI appears to parallel the severity of the hemodynamic derangement,[3,6,7] and because the elevated plasma levels tend to return to the normal range over the first 24 to 48 hours,[8,9] it is highly likely that sympathetic activation represents a reflex response to some hemodynamic deficit, e.g., a decrease in cardiac output, a reduction in tissue perfusion, a decrease in carotid/aortic pressure or pulse pressure, or some other as yet unrecognized reflex stimulation of the sympathetic nervous system.

Renin-angiotensin stimulation frequently occurs in patients with acute MI, particularly when left ventricular failure is present.[10,11] In the hypotensive patient, the increase in plasma renin activity may occur through renal sympathetic stimulation induced by baroreceptor unloading. A correlation between plasma norepinephrine and plasma renin activity supports this possibility.[8] The sympathetic response may be attenuated in patients who have had chronic heart failure in whom baroreceptor response to a decrease in blood pressure often is inhibited.[12] Even in the latter instance, however, renal baroreceptors controlling renin release still appear to be active and this may account for renin stimulation in the absence of sympathetic stimulation.[13]

TABLE I Physiologic Effects of Sympathetic Nervous System Stimulation

Increased myocardial contractility
Tachycardia
Atrial and ventricular arrhythmias
Coronary vasoconstriction
Decreased vascular compliance
Increased vascular resistance
Decreased venous capacitance
Regional blood flow redistribution
Myocardial hypertrophy

TABLE II Physiologic Effects of Renin-Angiotensin System Stimulation

Presynaptic stimulation of norepinephrine release
Decreased arterial compliance
Increased arterial resistance
Renal sodium retention
Renal potassium loss
Thirst
Regional blood flow redistribution
Myocardial hypertrophy

TABLE III Physiologic Effects of Antidiuretic Hormone (Vasopressin) Release

Increased free water reabsorption
Coronary vasoconstriction
Systemic vasoconstriction
Regional blood flow redistribution

TABLE IV Physiologic Effects of Atrial Natriuretic Peptide Release

Regional vasodilation and vasoconstriction
Inhibition of sympathetic, renin-angiotensin and vasopressin stimulation
Inhibition of renal sodium reabsorption

TABLE V Potential Deleterious Effects of Neurohormonal Stimulation of Acute Myocardial Infarction

Ventricular arrhythmias
Tachycardia
Reduced perfusion to ischemic myocardium
Increased ventricular filling pressure
Increased aotic impedance
Increased myocardial oxygen consumption
Reduced sodium and water excretion

Intrarenal mechanisms may contribute to renin stimulation, e.g., through macula densa response to reduction in sodium load. Furthermore, furosemide has a striking stimulatory effect on renin release, presumably through an intrarenal mechanism. Furosemide administered early in the course of acute MI may accentuate the neurohormonal response to the disease.[14]

An increase in plasma arginine vasopressin levels also is noted in patients with acute MI.[8,15] The mechanism of this apparently nonosmotic stimulus to vasopressin release is not fully understood, although morphine administration may play a role in some patients.

Atrial natriuretic peptide (ANP) levels also probably increase in response to an increase in left atrial pressure in the patient with acute MI.[16] Although it would be expected that ANP levels would decrease as the elevated left ventricular filling pressure normalizes after the acute event, studies of this phenomenon have not been reported.

EFFECTS OF NEUROHORMONAL STIMULATION

Reflex stimulation of the sympathetic nervous system (Table I) and renin-angiotensin system (Table II) results in vascular and cardiac effects aimed teleologically at supporting arterial pressure. Increases in arteriolar resistance and reductions in arterial compliance support mean arterial and systolic pressures in the face of a decreasing stroke volume. Support of arterial pressure may be particularly important in maintaining myocardial perfusion through a proximal stenosis in a coronary artery.[17]

A reflex increase in heart rate helps to maintain cardiac output, and an increase in myocardial contractility may augment stroke volume. Venoconstriction induced by neurohormonal stimulation shifts blood from the venous reservoir to the heart to augment cardiac filling and support cardiac contraction by a Frank-Starling mechanism. Volume effects may be accentuated by renal vasoconstriction and by angiotensin-induced aldosterone secretion. Finally, both norepinephrine and angiotensin may contribute to early myocardial protein synthesis that leads to myocardial hypertrophy.

Release of vasopressin and ANP has less well-established cardiovascular effects. The effect of vasopressin on free water excretion and on regional vascular tone are well known (Table III), but it is not clear if the blood levels achieved during acute MI are adequate to induce these physiologic effects.[18] Atrial peptide has direct effects on the kidney and as a vasodilator and vasoconstrictor, but it also may interfere with the response of the sympathetic nervous system, the renin-angiotensin system and arginine vasopressin release (Table IV).[19]

Although these neurohormonal responses may be appropriate and well-tolerated when the heart is normal, these physiologic effects may become deleterious in the setting of acute myocardial damage (Table V). The increase in vascular resistance and decrease in compliance raise the impedance to left ventricular ejection and may adversely affect left ventricular output. The increase in heart rate and contractility augment myocardial oxygen consumption and may aggravate ischemia. The increase in preload mediated by vasoconstriction and sodium retention may not produce an appropriate increase in stroke volume because the damaged ventricle is operating on a flat Frank-Starling curve. Furthermore, the increased preload may impede subendocardial perfusion and aggravate ischemia-induced pump dysfunction (Fig. 1). Finally, neurohormonal stimulation may contribute directly to

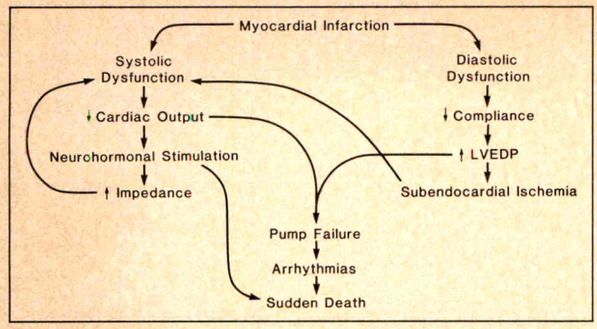


FIGURE 1. Vicious cycle of acute myocardial infarction eventuating in a pump failure or sudden death in part related to feedback loops involving both systolic and diastolic dysfunction. The adverse effect of vasoconstriction induced by neurohormonal stimulation is particularly related to systolic dysfunction that can be moderated by vasodilator therapy. Diastolic dysfunction in acute myocardial infarction is more transient and does not appear to respond favorably to vasodilator therapy. LVED = left ventricular end-diastolic pressure.

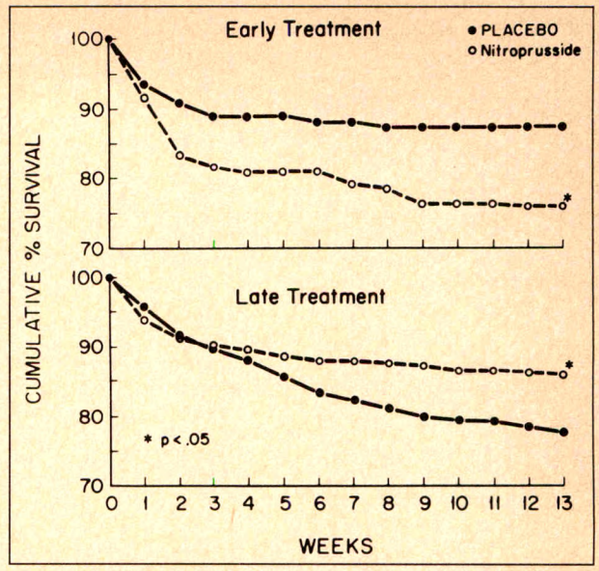


FIGURE 2. Mortality in patients randomized into the Veterans Administration trial within 9 hours after onset of acute myocardial infarction (Early Treatment) and after 9 hours (Late Treatment). (Reprinted with permission from *N Engl J Med.*[20])

ventricular arrhythmias that can precipitate ventricular fibrillation.

Because neurohormonally mediated vasoconstriction could have either favorable or unfavorable effects on the acutely infarcted ventricle, in 1975 we initiated a multicenter trial of short-term infusion of sodium nitroprusside in patients within 24 hours of acute MI.[20] Although therapy was not aimed at inhibiting the neurohormonal response, its goal was to counteract the vasoconstriction and thus lower impedance to left ventricular output. Because our preliminary studies indicated that nitroprusside infusion improved left ventricular global function without increasing heart rate,[21] this intervention appeared to be an appropriate probe to test whether vasoconstriction was good or bad in the setting of acute MI.

The multicenter trial was performed in 11 Veterans Administration Hospitals under sponsorship of the Veterans Administration Cooperative Studies Program. A total of 812 men with presumed acute MI were randomized after Swan-Ganz catheterization had confirmed the presence of an elevated pulmonary capillary wedge pressure >12 mm Hg. They received, in double-blind fashion, an infusion of sodium nitroprusside or placebo titrated to reduce the pulmonary wedge pressure to 60% of the control value or until systolic blood pressure decreased below a prescribed limit or a maximal dose had been reached. The infusion was continued for 48 hours with dosage adjustment if necessary to maintain the goal pressure. The mortality in these 2 treatment groups appeared to be significantly influenced by the timing of the institution of the infusion in relation to the course of the myocardial infarction. In patients in whom treatment was begun within 9 hours after the clinical onset of acute MI, nitroprusside had a statistically significant adverse effect on 13-week mortality (Fig. 2). In contrast, patients randomized and begun on infusion more than 9 hours from the onset of their infarct exhibited a statistically significant beneficial effect on mortality of nitroprusside infusion. This difference in survival between these 2 randomized groups persisted through 1 year of follow-up (Table VI).

We can speculate about the mechanism of this effect of sodium nitroprusside. One attractive possibility is that the patients randomized early into the trial represented a different population than those randomized later. Since an elevated pulmonary capillary wedge pressure was a prerequisite for randomization, and since pulmonary wedge pressure decreases progressively from its initial elevated levels after acute MI,[20,22] it is likely that many of the patients who underwent cardiac catheterization within the first few hours after their infarct had transiently elevated left ventricular filling pressure, which would have fallen into the normal range had they been seen later in the course of their illness. Thus, many of these patients who were randomized early may have had predominate diastolic dysfunction without much global systolic dysfunction; in this population, reduction of blood pressure may have had an adverse effect on myocardial perfusion without as much beneficial effect on left ventricular systolic function. In contrast, patients whose left ventricular

TABLE VI Mortality After Acute Myocardial Infarction in Veterans Administration Cooperative Study

	Nitroprusside			Placebo		
	No.	Deaths	%	No.	Deaths	%
13-Week Mortality						
All patients	407	69	17.0	405	77	19.0
≤9 hours	131	31	23.7	121	17	14.1
>9 hours	276	38	13.8	284	60	21.1
1-Year Mortality						
All patients	377	91	24.1	368	93	25.3
≤9 hours	126	36	28.6	112	23	20.5
>9 hours	251	55	21.9	256	70	27.3

filling pressures remained elevated more than 9 hours after the onset of MI probably had more severe global left ventricular systolic dysfunction in which the favorable effects of nitroprusside outweighed any possible adverse effects on coronary perfusion. In this group, persistent left ventricular diastolic hypertension in the placebo-treated patients may have contributed to persistent subendocardial ischemia that resulted in worsening of ventricular function and a higher mortality rate. In support of the suggestion that the patients who were randomized early were less sick than the patients randomized later is the observed mortality rate in the placebo groups. Mortality at 13 weeks was 50% higher in the group randomized more than 9 hours after onset of the infarct, and mortality at 1 year remained 33% higher in the group randomized late.

Although this study with sodium nitroprusside addressed only the systemic vasoconstrictor response as a manifestation of neurohormonal stimulation in acute MI, the data allowed us to propose a more rational understanding of the role of reflex vasoconstriction in the setting of acute MI. In milder forms of acute MI, when diastolic dysfunction is more prominent than systolic dysfunction, vasoconstriction supports coronary perfusion pressure but does not adversely affect left ventricular function. Inhibition of vasoconstriction in this setting is not beneficial. In more severe infarcts when systolic function is adversely affected, vasoconstriction aggravates left ventricular dysfunction and may contribute to progressive subendocardial ischemia and a worsening clinical state. In this latter situation, vasodilator therapy has a beneficial effect. Furthermore, when systolic dysfunction persists after MI, the clinical syndrome of chronic heart failure is accompanied by neurohormonal stimulation and vasoconstriction.[23] We now know that vasodilator therapy to counteract this vasoconstriction has a favorable effect on both left ventricular function and the course of the clinical syndrome.[24]

CONCLUSIONS

Thus, we can view neurohormonal responses in acute MI as both potentially beneficial and potentially harmful. Selection of the appropriate patient for the appropriate therapy is a challenge that can be met only by collection of appropriate physiologic data.

REFERENCES

1. Gazes PC, Richardson JA, Woods EF. Plasma catecholamine concentrations in myocardial infarction and angina pectoris. *Circulation 1959;19:657–661.*

2. Nadeau RA, de Champlain J. Plasma catecholamines in acute myocardial infarction. *Am Heart J 1979;98:548–554.*

3. Karlsberg RP, Cryer PE, Roberts R. Serial plasma catecholamine response early in the course of clinical acute myocardial infarction: relationship to infarct extent and mortality. *Am Heart J 1981;102:24–29.*

4. Esler M. Assessment of sympathetic nervous function in humans from noradrenaline plasma kinetics. *Clin Sci 1982;62:247–254.*

5. Russell RA, Crafoard J, Harris AS. Change in myocardial composition after coronary ejection. *Am J Physiology 1961;200:995–998.*

6. Valori C, Thomas M, Shillingford J. Free noradrenaline and adrenaline excretion in relation to clinical syndromes following myocardial infarction. *Am J Cardiol 1967;20:605–617.*

7. McDonald L, Baker C, Bary C, McDonald A, Restreaux N. Plasma catecholamines after cardiac infarction. *Lancet 1969;2:1021–1023.*

8. McAlpine HM, Morton JJ, Leckie B, Rumely A, Gillen G, Dargie HJ. Neuroendocrine activation after acute myocardial infarction. *Br Heart J 1988; 60:117–124.*

9. Francis GS, Cohn JN. Catecholamines in cardiovascular disease. *Upjohn Co., Kalamazoo, MI, 1987:20–32.*

10. Michorowski B, Ceremuzynski L. The renin-angiotensin-aldosterone system and the clinical cause of acute myocardial infarction. *Eur Heart J 1983;4:259–264.*

11. Vaney C, Waeber B, Turini G, Margalith D, Brunner HR, Perret C. Renin and the complications of acute myocardial infarction. *Chest 1984;86:40–43.*

12. Olivari MT, Levine TB, Cohn JN. Abnormal neurohormonal response to nitroprusside infusion in congestive heart failure. *JACC 1983;2:411–417.*

13. Levine TB, Olivari MT, Cohn JN. Dissociation of the responses of the renin-angiotensin system and sympathetic nervous system to a vasodilator stimulus in congestive heart failure. *Int J Cardiol 1986;8:973–977.*

14. Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. *Ann Intern Med 1985;103:1–6.*

15. Schaller MD, Nussberger J, Feihl F, Waeber B, Brunner HR, Perret C, Nicod P. Clinical and hemodynamic correlates of elevated plasma arginine vasopressin after acute myocardial infarction. *Am J Cardiol 1987;60:1178–1181.*

16. Hamosh P, Cohn JN. Left venricular function in acute myocardial infarction. *J Clin Invest 1971;50:523–533.*

17. Schwartz JS, Carlyle PF, Cohn JN. Effect of coronary arterial pressure on coronary stenosis resistance. *Circulation 1980;61:70–76.*

18. Goldsmith SR, Francis GS, Cowley AW, Goldenberg IF, Cohn JN. Hemodynamic effects of infused arginine vasopressin in congestive heart failure. *JACC 1986;8:779–783.*

19. Carson P, Carlyle PF, Cohn JN. Hemodynamic, neurohumoral, and renal response to atrial natriuretic peptide infusion in the conscious dog. In: Brenner BM, ed. Biologically Active Atrial Peptides. *New York: Raven Press, 1987:322–325.*

20. Cohn JN, Franciosa JA, Francis GS, Archibald D, Tristani F, Fletcher R, Montero A, Cintron G, Clarke J, Hager D, Saunders R, Cobb F, Smith R, Loeb H, Settle H. Effect of short-term infusion of sodium nitroprusside on mortality rate in acute myocardial infarction complicated by left ventricular failure. *N Engl J Med 1982;306:1129–1135.*

21. Franciosa JA, Guiha NH, Limas CJ, Rodriguera E, Cohn JN. Improved left ventricular function during nitroprusside infusion in acute myocardial infarction. *Lancet 1972;1:650–654.*

22. Franciosa JA, Guiha NH, Limas CJ, Paz S, Cohn JN. Arterial pressure as a determinant of left ventricular filling pressure after acute myocardial infarction. *Am J Cardiol 1974;34:506–512.*

23. Cohn JN, Mashiro I, Levine TB, Mehta J. Role of vasoconstrictor mechanisms in the control of left ventricular performance of the normal and damaged heart. *Am J Cardiol 1979;44:1019–1022.*

24. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH, Goldman S, Cobb FR, Shah PM, Saunders R, Fletcher RD, Loeb HS, Hughes VC, Baker B. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study (V-HEFT). *N Engl J Med 1986; 314:1147–1152.*

Neuroendocrine Activation in Acute Myocardial Infarction

T. Barry Levine, MD

Recent research indicates that neurohormonal responses after myocardial infarction may predict patient outcome, and alteration of this process may change etiologic factors and strengthen positive prognosticators. Because there are clinical similarities between acute myocardial infarction and heart failure, there appears to be justification for a unified treatment approach (i.e., therapies that have proved beneficial in the treatment of myocardial infarction have also showed promise in the treatment of heart failure). Conversely, some therapies that have benefited the patient with heart failure may benefit the patient who has had a myocardial infarction. For example, angiotensin-converting enzyme inhibitors have been proven to blunt detrimental neurohormonal activity seen after myocardial infarction. These therapies promise to reduce complications and improve survival.

(Am J Cardiol 1990;65:32 I–34 I)

A myocardial infarction is a stress to the entire cardiovascular system that has both myocardial and systemic consequences, and the neurohormonal responses to myocardial infarction are maladaptive attempts to readjust to the various aspects of the destabilizing event. Myocardial injury triggers increased activity of both the sympathetic nervous system and the renin-angiotensin system, and recent studies indicate that patient outcome is predicted by the severity of these neurohormonal responses. However, modification of these responses may alter the clinical course of the underlying disease process.

Many factors theoretically participate in the increased neuroendocrine response to acute myocardial infarction. Pain and anxiety increase adrenomedullary release of epinephrine and norepinephrine. Decreased cardiac output and hypotension stimulate peripheral sympathetic activity and reduce renal blood flow activating the renin-angiotensin system. Regionally, myocardial necrosis releases norepinephrine stores from the infarcted area. Furthermore, coronary insufficiency resulting in ischemia but not necrosis also releases myocardial norepinephrine. The recent discovery of an intact renin-angiotensin system within the heart also raises the possibility of local activation of this endocrine system. The integrated action of these 2 systems on the myocardium and at the periphery may result in mutual stimulation.

There is considerable evidence for increased neuroendocrine activity in both the experimental infarction models and the clinical setting of acute myocardial infarction. A number of studies have shown that myocardial necrosis leads to release of norepinephrine stores in necrotic myocardial tissue.[1–3] Infarction, however, is not a prerequisite for this phenomenon. Muntz et al[4] evaluated alterations in myocardial catecholamines during early myocardial ischemia in dogs. The left anterior descending artery was ligated and regional release of myocardial norepinephrine vs regional coronary blood flow was assayed. At 1 hour after ligation, myocardial catecholamines were identical in all regions of the myocardium. By 3 hours, however, a significant decrease in catecholamines was noted in the endocardium of the ischemic region. This was not seen in the less ischemic epicardial region. The investigators noted that there was a redistribution of catecholamines from nerve terminals to other interstitial tissue compartments. Thus, ischemia before infarction resulted in release of myocellular norepinephrine to surrounding interstitial spaces. Potential toxic effects of excessive extracellular norepinephrine was illustrated by observations of Gavros et al.[5] Intravenous infusions of norepinephrine in rabbits resulted in extensive, often confluent, multifocal myocardial necrosis.

From the Heart Failure and Cardiac Transplant Program, Detroit, Michigan.

Address for reprints: T. Barry Levine, MD, Heart Failure and Cardiac Transplant Program, Henry Ford Hospital, Heart and Vascular Institute, 2799 W. Grand Boulevard, Detroit, Michigan 48202.

Increased activity of the renin-angiotensin system is also seen after myocardial infarction. Reduction in cardiac output resulting in decreased renal blood flow and renal perfusion pressure will increase the activity of this homeostatic system.[6,7] Furthermore, increased renal sympathetic nerve traffic will also increase renin release.[8] Finally, there is evidence of an intact renin-angiotensin system within the heart. Ertl[9] demonstrated that a 30-second occlusion of the coronary artery in dogs results in increased renin activity and angiotensin II levels. The increased vasoconstriction mediated by enhanced angiotensin II activity resulted in increased afterload and thus myocardial oxygen demand, potentiating the left ventricular (LV) dysfunction seen in an acute myocardial infarction. The intriguing observations of Gavros et al[5] in rabbits, that intravenous angiotensin II caused extensive myocardial necrosis identical to that seen with norepinephrine, raises the possibility of further myocardial damage mediated either directly or indirectly by norepinephrine.

There is considerable clinical evidence that increased neuroendocrine activity is detrimental to patients after a myocardial infarction. These vasoconstrictor mechanisms increase myocardial oxygen demand, and reduce supply by vasoconstricting the coronary bed and reducing blood flow. They therefore might be expected to promote infarct expansion, recurrent ischemia, reinfarction, heart failure and arrhythmias. Early work was performed by Prakash et al[10] measuring urinary catecholamines in patients after acute myocardial infarction. They demonstrated a correlation between neurohormonal activity and subsequent development of LV failure, life-threatening arrhythmias, shock and death. In fact, patients with complicated postmyocardial infarction had significantly higher urinary catecholamines than patients with uncomplicated myocardial infarction. These early observations led to the concept that increased catecholamines were predictors for the severity of infarction and the clinical outcome. That this increased sympathetic activity participated in the pathophysiology of acute myocardial infarction was demonstrated by Kalsberg et al.[11] They found increased levels of plasma norepinephrine and epinephrine within 4 hours of the onset of myocardial infarction before any creatine phosphokinase release. There was a direct correlation between mean epinephrine, norepinephrine and peak epinephrine levels, and levels of creatine phosphokinase generated by the myocardial infarction. During follow up, patients with the highest levels of circulating catecholamines were also those with the poorest prognosis. These investigators logically suggested that the magnitude of neurohormonal activation early in the course of an acute myocardial infarction played a role in the extent of myocardial damage and eventual mortality. Vaney et al[12] also demonstrated increased plasma norepinephrine and epinephrine levels after myocardial infarction. They noted the correlation between the size of the infarction and the level of circulating catecholamines. Furthermore, they extended their observations to the renin-angiotensin system. They found that plasma renin activity also increased after myocardial infarction. In their series, patients with the greatest increase in neuroendocrine activity, after a myocardial infarction, were those most likely to have cardiogenic shock or ventricular fibrillation.

Clearly, the larger the myocardial infarction, the greater the neuroendocrine response and the worse the prognosis. However, the increased neuroendocrine activity, after an infarction, can independently contribute to infarct expansion and extension and worsening prognosis.

APPROACHING A MYOCARDIAL INFARCTION AS "TELESCOPED HEART FAILURE"

One is struck by the apparent pathophysiologic similarities of acute myocardial infarction and heart failure. In both situations pump dysfunction is present. Both heart failure and myocardial infarction result in depleted myocardial catecholamine stores. In both, an inappropriate peripheral vasoconstriction is seen mediated by increased activity of the renin-angiotensin system and an increased sympathetic tone. Finally, arrhythmias are frequent occurrences in both situations, as is sudden death.

Thus, acute myocardial infarction and stable heart failure may be viewed as a physiologic continuum, and myocardial infarction is essentially "telescoped heart failure." This unifying physiologic outlook leads to potential unification in therapy. In each clinical situation the therapy that benefits one disease seems to hold promise for the other.

Beta blockade is an accepted therapy after myocardial infarction. A number of placebo controlled trials have shown that β blockade improves survival and reduces reinfarction after a myocardial infarction.[13–15] This observation was also underscored in the recent Thrombolysis in Myocardial Infarction II trial.[16] In this study a subset of patients, after thrombolytic therapy, were randomized to metoprolol either immediately after infarction or 6 days later. The results of this study showed that those receiving metoprolol immediately after myocardial infarction had a lower incidence of reinfarction and recurrence of ischemia. Interestingly and analogously, there is increasing interest in the use of β blockade to treat congestive heart failure.[17] One randomized placebo-controlled trial showed these drugs to improve conditions in patients with primary cardiomyopathy both functionally and symptomatically.[18] Why these drugs might benefit patients with heart failure is unknown. Perhaps it is the myocardial protection of β blockade on further catecholamine-mediated damage, or it might be a resetting of myocardial β receptors leading to improved cardiac function.

Conversely, the converting enzyme inhibitors are accepted therapy for the treatment of heart failure.[19–21] These drugs have shown symptomatic and functional improvement in patients, and more recently in survival. The Coopertive North Scandanavian Enalapril Survival Study examined patients with end-stage congestive heart failure.[22] Most patients had ischemia as the underlying cause of LV dysfunction. The study showed that patients randomized to enalapril had significantly greater 6-month and 1-year survival then those taking placebo. Thus, it has been shown experimentally that a converting enzyme inhibitor preserves myocardial contractile func-

tion in an ischemic segment stressed by either tachycardia or reperfusion.[9] The ability of captopril to protect ischemic myocardium may represent a reduction in myocellular toxicity mediated by angiotensin II. In a recent study, Pfeffer et al[23] showed that after myocardial infarction, patients randomized to a converting enzyme inhibitor had an increase in exercise capacity 3 months to 1 year after myocardial infarction when compared with a placebo-controlled cohort despite the presence of LV dysfunction. Thus, the lessons learned in the therapy of end-stage congestive heart failure appears to apply to acute myocardial infarction (telescoped congestive heart failure), and these preliminary studies offer exciting promise to patients with ischemic heart disease. The ability to blunt the neurohormonal activity seen in an acute infarction promises to reduce the complications seen in these patients and improve survival. Aggressive pharmacologic therapies are an essential and appropriate complement to the aggressive interventional strategies pursued to treat myocardial infarctions.

REFERENCES

1. Mathes P, Gudbjarnason S. Changes in norepinephrine stores in the canine heart following experimental myocardial infarction. *Am Heart J 1971;18:211–219.*

2. Paessens R, Borehard F. Morphology of cardiac nerves in experimental infarction of rat hearts. I. Fluorescence microscopical findings. *Virchows Arch 1980; 386:265–278.*

3. Schomig A, Dart AM, Dietz R, Moyer E, Kubler W. Release of endogenous catecholamines in the ischemic myocardium of the rat. Part A: locally mediated release. *Circ Res 1984;55:689–701.*

4. Muntz KH, Hagler HK, Boulos HJ, Willerson JT, Buja LM. Redistribution of catecholamines in the ischemic zone of the dog heart. *Am J Pharmacol 1984;144:64–78.*

5. Gavros H, Kremer D, Brown JJ, Gray B, Lever AF, MacAdam RF, Medina A, Morton JJ, Robertson JIS. Angiotensin and norepinephrine induced myocardial lesions: experimental and clinical studies in rabbits and man. *Am Heart J 1975;89:321–332.*

6. Farhi ER, Cant JR, Burger AC. Interactions between intrarenal epinephrine receptors and the renal baroreceptor in the control of PRA in conscious dogs. *Circ Res 1982;50:447–485.*

7. Brown JJ, Davis DL, Lever AF, Robertson JIS. Plasma renin concentration in human heart failure. *Br Med J 1965;2:144–148.*

8. Keeton TK, Campbell WB. The pharmacologic alteration of renin release. *Pharmacol Rev 1980;32:81–227.*

9. Ertl G. Coronary vasoconstriction in experimental myocardial ischemia. *J Cardiovasc Pharmacol 1987;9:suppl 12:S9–S17.*

10. Prakash R, Parmley WW, Horvat M, Swan HJC. Serum cortisol, plasma free fatty acids, and urinary catecholamines as indicators of complications in acute myocardial infarction. *Circulation 1972;45:736–745.*

11. Karlsberg RP, Gryer PE, Roberts R. Serial plasma catecholamine response early in the course of clinical acute myocardial infarction: relationship to infarct extent and mortality. *Am Heart J 1965;16:230–237.*

12. Vaney C, Waeber B, Turini G, Margoleth D, Brunner HR, Perret C. Renin and the complications of acute myocardial infarction. *Chest 1984;8:40–43.*

13. Beta-Blocker Heart Attack Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA 1982;247:1707–1714.*

14. Hjalmarson A, Elmfeldt D, Herlitz J, Holmberg S, Malek I, Nyberg G, Ryden L, Swedberg K, Vedin A, Waagstein F, Waldenstrom A, Waldenstrom J, Wedel H, Wilhelmsen L, Wilhemsson C. Effect of mortality of metroprolol in acute myocardial infarction. *Lancet 1981;2:823–827.*

15. The Norwegian Multicenter Study Group: Timolol induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med 1981;304:801–807.*

16. The TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction. *N Engl J Med 1989;320:618–627.*

17. Swedberg K, Hjalmorson A, Waagsteen F, Wallentin I. Beneficial effects of long-term beta-blockade in congestive cardiomyopathy. *Br Heart J 1980;44:117–133.*

18. Enselmeier RS, O'Connell JB, Walsh R, Rad N, Scanlon PJ, Gunnar RM. Improvement in symptoms and exercise tolerance by metoprolol in patients with dilated cardiomyopathy: a double-blind, randomized, placebo-controlled trial. *Circulation 1985;72(3):536–546.*

19. Captopril Multicenter Group. A placebo-controlled trial of captopril in refractory chronic congestive heart failure. *JACC 1983;2:755–763.*

20. Levine TB, Olivari MT, Simon AB, Cohn JN. Angiotensin converting enzyme inhibition in congestive heart failure; a comparison of captopril and enalapril. *Am J Med 1986;81:36–39.*

21. Giles TD, Katz R, Sullivan JM. Short-and-long activating angiotensin-converting enzyme inhibitors: a randomized trial of lisinopril versus captopril in the treatment of congestive heart failure. *JACC 1989;13:1240–1250.*

22. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: Results of the Cooperative North Scandinavian Enalapril Survival Study. *N Engl J Med 1987;316:1429–1435.*

23. Pfeffer MA, Gervasio A, Lamas MD, Vaughan DE, Porisi AF, Braunwald E. Effect of captopril on progressive ventricular dilatation after myocardial infarction. *N Engl J Med 1988;319:80–86.*

Protection of the Myocardium During Myocardial Infarction: Pharmacologic Protection During Thrombolytic Therapy

James T. Willerson, MD, and L. Maximilian Buja, MD

The most effective way to protect injured myocardium during the early phases of evolving myocardial infarction is with reperfusion. However, reperfusion may induce further myocardial injury. Alterations in the major determinants of myocardial oxygen demand, including increases in heart rate, contractile state and myocardial wall tension may also increase infarct size. An understanding of the basic mechanisms involved in the evolution of myocardial injury during myocardial infarction is important to the development of protective strategies that may reduce infarct size or attenuate reperfusion-induced myocardial injury, or both. Selective calcium antagonists, β blockers, and phospholipase antagonists or inhibitors may reduce infarct size in association with early reperfusion. Reperfusion injury may be attenuated by free radical scavengers and calcium antagonists. Reinfarction, after the initial event, may ultimately be reduced in frequency by pharmacologic strategies that interfere with platelet adhesion, aggregation, and mediator release from activated platelets and white cells that promote further platelet aggregation or induce coronary artery vasoconstriction. Included among protective strategies are thromboxane receptor antagonists and synthesis inhibitors, serotonin receptor antagonists, possibly leukotriene synthesis inhibitors or receptor antagonists, and aspirin. Future clinical trials should test the combined efficacy of reperfusion and selected pharmacologic strategies that alter calcium accumulation in the injured myocardium, diminish the injurious effects of β- and α-adrenergic mechanisms and oxygen-derived free radicals on injured myocytes, and prevent reocclusion mediated by platelets and platelet mediators.

(Am J Cardiol 1990;65:35 I–41 I)

From the Department of Internal Medicine (Cardiology Division) and Pathology, University of Texas, Southwestern Medical Center, Dallas, Texas. This work was supported in part by Ischemic SCOR HL17669 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland, and the Moss Heart Fund, Dallas, Texas.

Address for reprints: James T. Willerson, MD, University of Texas Medical School, Department of Internal Medicine, 6431 Fannin, Room 1.150, Houston, Texas 77030.

Myocardial infarction occurs with increases in myocardial oxygen demand, but far more often with decreases in myocardial oxygen delivery associated with temporary and permanent coronary artery occlusions.[1–3] Recent studies have established that the most effective way to limit infarct size is with myocardial reperfusion early in the evolution of the infarction.[4,5] However, reperfusion itself may contribute to myocardial injury, including cellular and vascular endothelial swelling and interstitial edema and hemorrhage.[6–8] Calcium accumulation occurs in injured myocytes with altered membrane permeability and may activate destructive cellular processes, including phospholipases,[9–11] and impair mitochondrial oxidative phosphorylation and the generation of high energy phosphates.[12,13] Thirty minutes to 1 hour of coronary artery occlusion in canine and feline models causes an increase in β- and α-adrenergic receptor numbers on reversibly injured myocytes with no change in agonist affinity.[14–18] Catecholamines leak from their storage depots during the same time period and injured myocytes are bathed in relatively high concentrations of catecholamines, potentially resulting in arrhythmias, myocyte injury, cellular calcium overloading and membrane injury.[19,20] This report reviews basic mechanisms involved in myocyte injury during evolving myocardial infarction and suggests protective strategies based on an understanding of pathophysiologic mechanisms involved in cellular injury during evolving myocardial infarction.

GENERAL MECHANISMS

Myocardial infarcts occur with temporary coronary artery occlusion and reperfusion and with fixed or permanent coronary artery occlusion. On occasion, myocardial infarcts occur when myocardial oxygen demand is increased above the ability of narrowed coronary arteries to deliver oxygen, such as with increases in heart rate, contractile state or myocardial wall tension.[1–3] Alternatively, myocardial infarcts (usually non-Q-wave or subendocardial infarcts) may also occur when myocardial oxygen delivery is reduced by systemic arterial hypotension or with very severe systemic arterial hypertension or by metabolic abnormalities in which myocardial substrate availability is reduced, or by a combination of these, e.g., in hypoglycemia or severe acidosis.[1]

Irreversible myocardial injury develops within 20 minutes and during longer periods of critical reduction in myocardial oxygen delivery. There is a wavefront of evolving myocardial necrosis from endocardium to epi-

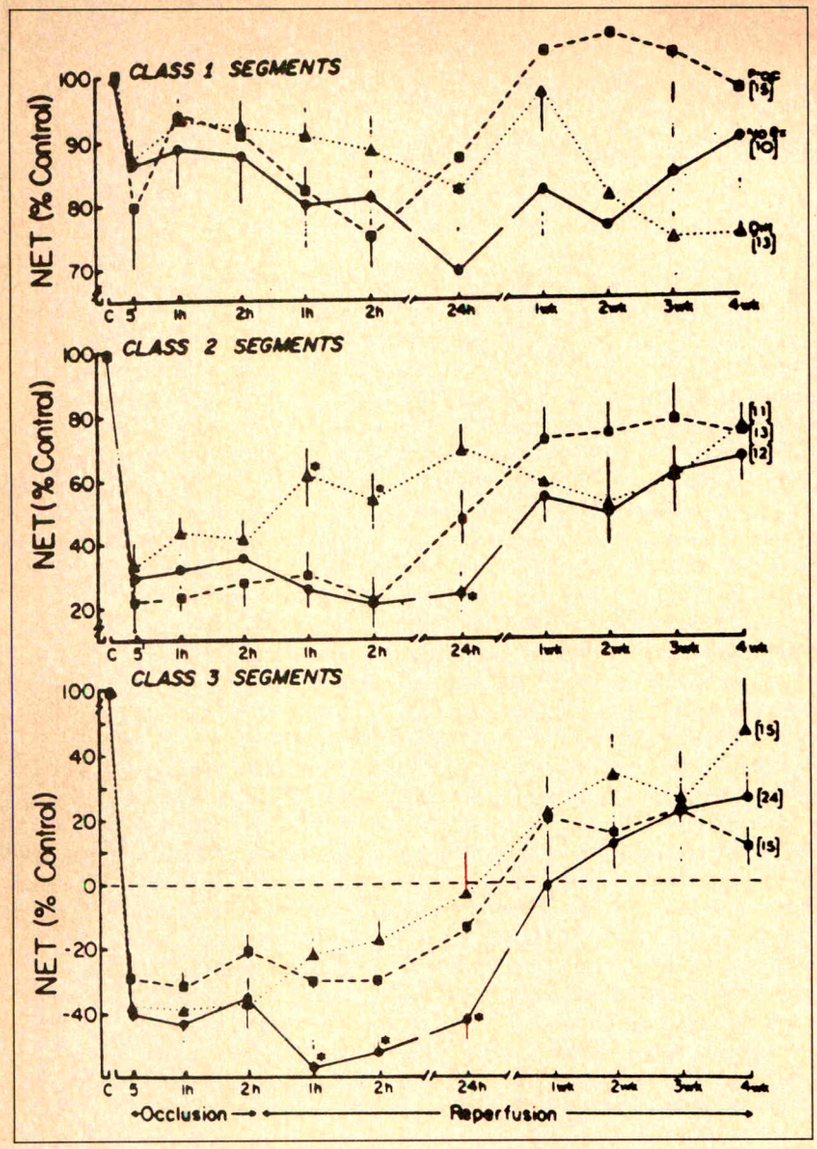


FIGURE 1. Changes in NET expressed as a percentage of control value during 2 hours of left anterior descending coronary artery occlusion and 1 month of reperfusion in dogs with 2 hours of temporary coronary artery occlusion followed by 1 month of reperfusion. * Significant difference vs other 2 treatment groups ($p < 0.05$ analysis of variance, Duncan's multiple range test). The numbers in *parentheses* represent the number of segments in each class and treatment group. These segmental functional studies were obtained in chronically instrumented dogs with coronary artery occlusions lasting 2 hours and with treatment with either propranolol (Prop), placebo (No Rx) or diltiazem (Dilt). Reperfusion itself resulted in as much recovery of left ventricular systolic wall thickening (NET) at sites of mild dysfunction during the coronary occlusion (*top panel*), at sites of moderate segmental dysfunction (*middle panel*), and at sites of severe segmental dysfunction (*bottom panel*) as reperfusion at 2 hours with diltiazem or propranolol. (Reproduced from *Circulation 1985;72:423*, by permission of the American Heart Association).

cardium that occurs during the initial 6 hours after coronary artery occlusion in canine models.[21] Thirty minutes to ≥1 hour of permanent coronary artery occlusion is associated with small increases in cellular calcium concentration, 50 to 80% increases in the number of β- and α-adrenergic receptors on injured myocytes with no change in agonist affinity, phospholipase activation with consequent membrane phospholipid degradation, and marked reduction in high energy phosphate concentration.[9–18] A severe local metabolic acidosis develops, and sodium potassium adenosine triphosphatase activity on injured myocytes is depressed with a consequent accumulation of cellular sodium, extrusion of potassium, and increase in injured myocyte calcium concentration, at least partly as a consequence of sodium-calcium exchange.[6] These cellular alterations are progressive with time. One to 3 hours after coronary artery occlusion, catecholamines leak from their myocardial storage depots and injured myocytes are exposed to relatively high concentrations of catecholamines.[19,20] Myocardial reperfusion after temporary coronary artery occlusion of 30 minutes or longer results in cellular and interstitial edema and substantial increases in cellular calcium concentration.[6] Periods of temporary coronary artery occlusion lasting more than 1 hour followed by reperfusion may be associated with myocardial hemorrhage.[6] The longer the duration of coronary artery occlusion, the less salvage of myocardium is achieved by reperfusion.[4,5,21]

Thus, to limit the extent of myocyte injury during myocardial infarction, reperfusion at an early period in the evolution of cellular injury is required, i.e., usually within the first 2 hours.[4,5] Theoretically, interventions that antagonize intrinsic cellular alterations, which contribute to the development of irreversible injury in myocardial cells during ischemic injury and evolving myocardial infarction (including calcium accumulation, enhanced adrenergic influences, phospholipase activation and, with reperfusion, cellular and endothelial edema, myocardial hemorrhage and free radical generation) might enhance the protection of injured myocytes.

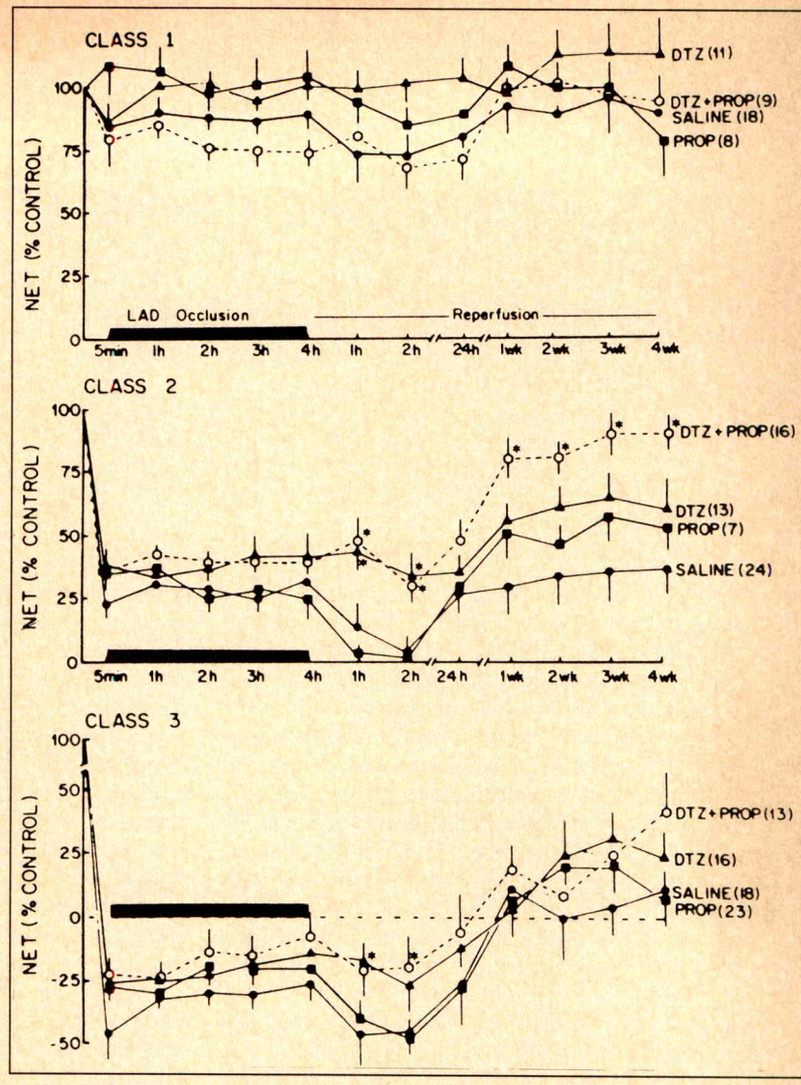


FIGURE 2. Changes in NET (left ventricular segmental systolic wall thickening) during 4 hours of left anterior descending artery (LAD) occlusion and 1 month of reperfusion in group II dogs. *Asterisks* during early reperfusion in class 2 segments denote significance vs the other 2 treatment groups. *Asterisks* at 1 to 4 weeks after reperfusion denote a significant difference between propranolol plus diltiazem (DTZ) vs saline-treated groups only. In class 3 segments, *asterisks* denote that the value for diltiazem-treated dogs alone was significantly different compared with the propranolol- (PROP) or saline-treated dogs at 1 hour after reperfusion and for propranolol- plus diltiazem-treated dogs alone at 2 hours after reperfusion. (Reproduced from *Circulation 1985;72:423,* by permission of the American Heart Association).

SELECTED PHARMACOLOGIC INTERVENTIONS THAT ANTAGONIZE CELLULAR DESTRUCTIVE PROCESSES DURING EVOLVING MYOCARDIAL INFARCTION

With appropriate pharmacologic therapy, one may be able to prolong the window of time beyond which reperfusion may not ordinarily be protective.[4,5]

Temporary coronary artery occlusion and reperfusion: Reperfusion after temporary coronary artery occlusion, lasting ≤2 hours, preserves segmental function and reduces infarct size at sites of moderate segmental dysfunction (Fig. 1).[4,5] In animal models, myocardial infarction is largely confined to the subendocardium, or a non-Q-wave infarct, when reperfusion is provided within 2 hours of experimental coronary artery occlusion.[4] However, if coronary artery occlusion lasts ≥4 hours, reperfusion does not reduce infarct size or preserve segmental function at left ventricular sites of moderate ischemic dysfunction in the canine heart (Fig. 2).[4] Thus, in the canine heart, the window of time beyond which myocardial reperfusion does not reduce infarct size and protect segmental ventricular function is between 2 and 4 hours of coronary artery occlusion.[4,5] However, if one administers a β blocker and a calcium antagonist beginning 90 minutes after temporary coronary artery occlusion, the combination of a selected calcium antagonist (diltiazem) and a β blocker (propranolol), in combination with reperfusion, reduces infarct size and protects segmental ventricular function (Fig. 2).[22,23] Neither diltiazem nor propranolol protected segmental function in these studies, although some reduction in segmental infarct size was found at sites of moderate left ventricular dysfunction when the β blocker or calcium antagonist was combined with reperfusion (Table I).[22] Reperfusion with a β blocker, after 1 hour of coronary artery occlusion, prevents β-adrenergic agonist-induced increases in ischemic region cyclic adenosine monophosphate and activated phosphorylase concentrations.[15]

Protection by phospholipase inhibitors: In cultured neonatal rat myocytes, metabolic inhibitors, such as cyanide and deoxyglucose or iodoacetate, cause high energy phosphate depletion and increases in myocyte calcium concentration in association with membrane phospholip-

TABLE I Macrohistochemically Determined Infarct Size (g/100 g)

Hours of Occlusion	Variable	Saline	Propranolol	Diltiazem	Propranolol and Diltiazem
2 (group II)	Risk Total LV	19.7 ± 1.5	23.8 ± 2.3	18.4 ± 1.9	
	Infarct Risk	22.7 ± 4.9	23.0 ± 5.8	22.0 ± 4.1	
	Infarct Total LV	5.0 ± 0.9 (n = 13)	5.1 ± 1.3 (n = 6)	4.8 ± 1.1 (n = 7)	
4 (group III)	Risk Total LV	19.8 ± 2.4	19.3 ± 2.1	18.9 ± 1.8	28.0 ± 3.9
	Infarct Risk	29.2 ± 7.4	21.3 ± 3.6	15.7 ± 4.9	8.9 ± 5.4
	Infarct Total LV	7.1 ± 1.7* (n = 11)	4.3 ± 0.8*† (n = 9)	2.9 ± 0.9† (n = 9)	2.1 ± 1.0† (n = 8)

Values with different superscripts are significantly different from one another by 1-way analysis of variance and Duncan's multiple range test. Group II dogs had 2 hours of temporary coronary artery occlusion followed by 1 month of reperfusion. Group III dogs had temporary coronary artery occlusions of 4 hours followed by 1 month of reperfusion.
LV = left ventricle.
Adapted from *Circulation*.[22]

id degradation.[24] Phospholipase inhibitors added to metabolically injured myocytes allow better recovery of high energy phosphate concentrations and protection from marked excesses in cellular calcium loading.[24]

Reperfusion-induced myocardial injury: With reperfusion after periods of temporary coronary artery occlusion lasting 30 minutes to 1 hour, reactive oxygen species accumulate in injured myocardium and may contribute to myocardial cellular or vascular injury, or both.[25,26] Selected oxygen free radical scavengers prevent or attenuate transient myocardial dysfunction associated with reperfusion after brief periods of coronary artery occlusion and reduce the extent of myocardial injury associated with reperfusion.[26] Similarly, selected calcium antagonists also prevent or attenuate transient myocardial dysfunction associated with reperfusion after temporary coronary artery occlusion ("myocardial stunning").[27]

Reocclusion after temporary coronary artery occlusion and reperfusion: With endothelial injury at sites of coronary artery stenosis, platelets adhere and aggregate and release selective mediators, especially thromboxane A_2 and serotonin, that promote further platelet aggregation and dynamic coronary artery vasoconstriction (Fig. 3 and 4).[28–40] Reocclusion after reperfusion therapy appears to be platelet mediated and may be prevented or markedly delayed by the administration of a platelet monoclonal antibody against the glycoprotein IIB-IIIA receptor[37] or with the combined administration of thromboxane and serotonin receptor antagonists (Fig. 5).[39,40] Thus, platelet attachment and aggregation and release of thromboxane A_2 and serotonin are important in mediating reocclusion after thrombolytic therapy in selected animal models, and reocclusion may be prevented or delayed by using appropriate receptor antagonists or antiplatelet antibodies.

Clinical trials with reperfusion and selected pharmacologic intervention: Several recent studies have suggested that the administration of selected β blockers, including metoprolol, early in the evolution of myocardial infarction and continued thereafter reduces the risk of death and of nonfatal myocardial infarction in selected patients.[41,42] A recent study sponsored by the National Heart, Lung, and Blood Institute (Thrombolysis in Myocardial Infarction Trial-2) evaluated the influence of tissue plasminogen activator alone and in combination with a β blocker in patients with acute myocardial infarction with symptoms lasting <3 hours.[41] The β blocker with tissue plasminogen activator reduced the risk of recurrent

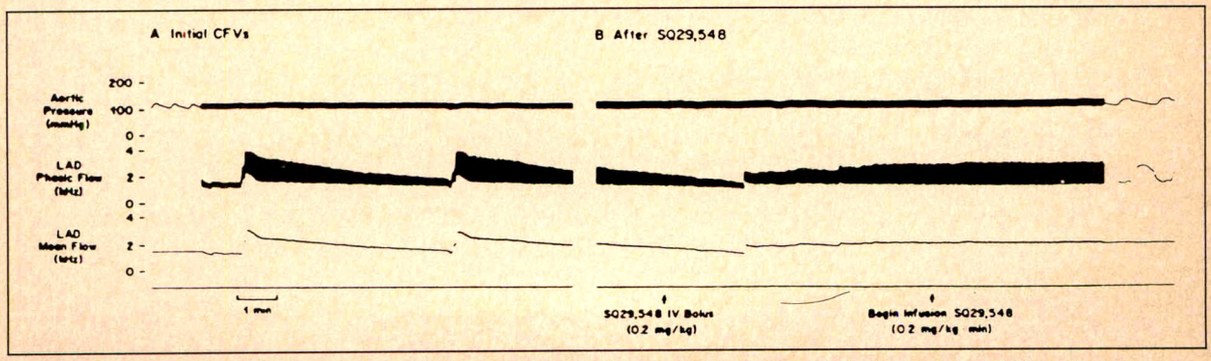


FIGURE 3. A representative recording from a dog with cyclic flow variations (CFVs) and abolition of the CFVs with the thromboxane receptor antagonist (SQ29,548). *Panel A*, initial CFVs. Note the reccurring pattern of decline and restoration of mean and phasic left anterior descending arterial (LAD) flow. *Panel B*, a normal pattern of flow restored minutes after administration of SQ29,548. (Reproduced from *Circ Res 1986;59:572*, with permission of the American Heart Association).

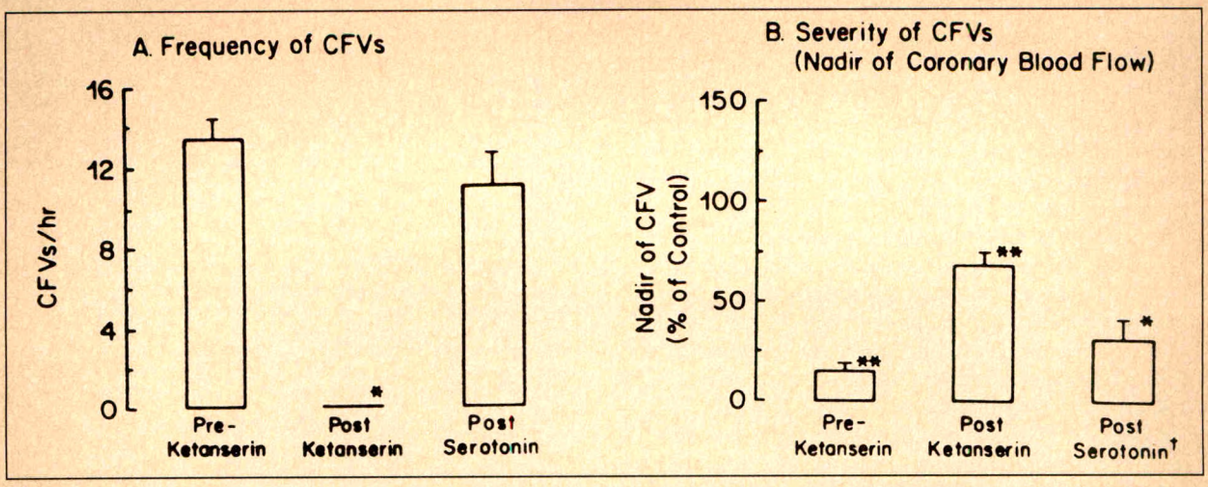


FIGURE 4. ***A,*** **the number of cyclic flow variations (CFVs) per hour in dogs during a control period, after abolition of CFVs by the serotonin receptor antagonist, ketanserin, and after reestablishment of CFVs during the infusion of serotonin into the left atrium.** ***B,*** **the severity of CFVs, obtained by averaging the 2 lowest mean flow velocity values (nadirs) as a percentage of control, unconstricted blood flow velocity over a 30-minute interval, are shown for control CFVs and after ketanserin abolished CFVs. † The mean flow velocity nadir in serotonin-restored CFVs was taken as a percentage of mean flow velocity after infusion of serotonin but before the restoration of CFVs. (** $p < 0.05$, **significantly different from control, unconstricted coronary blood flow velocity; * $p < 0.05$, **significantly different from coronary blood flow velocity during infusion of serotonin and before CFVs were restored.) These studies were performed in anesthetized, open-chest dogs with severe coronary artery stenosis and endothelial injury, and they demonstrate that the serotonin receptor antagonist, ketanserin, markedly reduces the frequency of CFVs and the administration of serotonin reestablishes the CFVs thereafter. (Reproduced from** ***Circulation 1989;73:576,*** **by permission of the American Heart Association.)**

nonfatal reinfarction and myocardial ischemia.[41] The protective effect of β blockers without intrinsic sympathomimetic effects in the hours to months to years after myocardial infarction is most likely related to the prevention of hemodynamic variable alterations that may lead to myocardial infarction or may directly protect against catecholamine-induced arrhythmias.[43–45]

Permanent coronary artery occlusion: If the period of coronary artery occlusion lasts several hours, protective interventions are relatively limited in their ability to prevent progressive myocardial necrosis and the loss of segmental ventricular function. Selected pharmacologic interventions, including β blockers, hyaluronidase, increases in serum glucose or serum osmolality caused by hypertonic mannitol administration, may reduce the extent of infarction when given as pretreatment or very early after coronary artery occlusion when the period of coronary artery occlusion is relatively short, i.e., 40 minutes to 1 hour.[1,46] However, longer periods of coronary artery occlusion usually require reperfusion to limit infarct size and protect segmental function.

FUTURE CLINICAL STUDIES THAT ARE NEEDED

Reperfusion, when accomplished early in patients with evolving anterior Q-wave infarcts may limit infarct

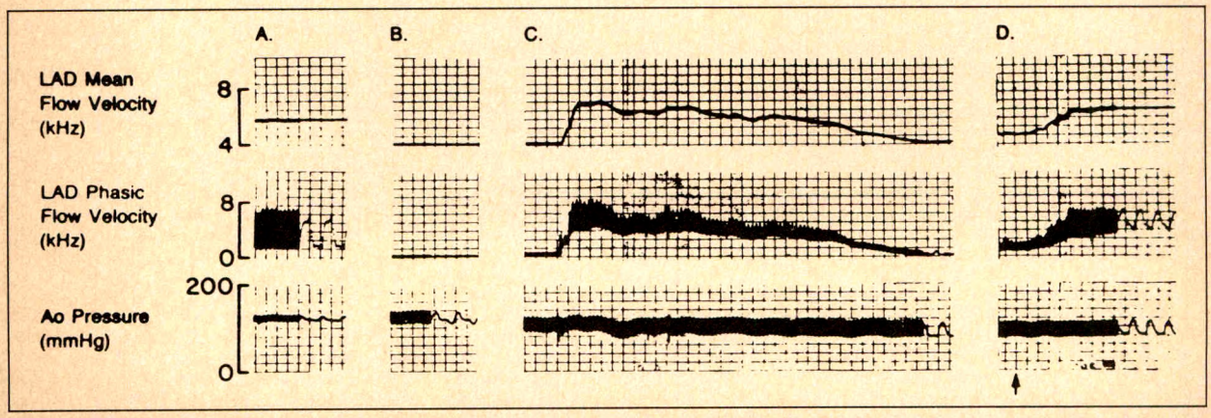


FIGURE 5. In an anesthetized, open-chest dog with a copper coil positioned in the proximal left anterior descending artery (LAD), an intracoronary thrombus developed within a few minutes (*panels A* and *B* in the *top 2 panels*). Subsequently, the administration of tissue plasminogen activator intravenously (80 μg bolus followed by 8 μg/kg/min) reestablished coronary blood flow (*panel C* in the *top 2 panels*). However, coronary artery thrombosis developed once again and flow was restored by the simultaneous administration of a thromboxane and serotonin receptor antagonist (*panel D* in the *top 2 panels*). (Reproduced from *Circulation 1988;77:678–684,* by permission of the American Heart Association.)

size and protect segmental and global ventricular function.[47,48] Early reperfusion may also be protective,[49] with inferior infarcts that involve the lateral, right ventricular or true posterior surface, in addition to the diaphragmatic wall. In future clinical studies, it will be important to learn whether selected therapy that antagonizes cellular destructive processes caused by myocardial ischemia will complement and be additive to reperfusion in the reduction of infarct size and preservation of ventricular function. Pharmacologic strategies that should be tested singly and in combination include some of the following: (1) free radical scavengers; (2) phospholipase inhibitors; (3) selected β blockers without intrinsic sympathomimetic activity; (4) selected calcium antagonists; and (5) pharmacologic strategies aimed at preventing reocclusion after thrombolysis, including serotonin and thromboxane receptor antagonists and monoclonal antibodies directed against platelet aggregation and adhesion.

REFERENCES

1. Willerson JT. Acute myocardial infarction. In: Wyngaarden JB, Smith LH Jr, eds. Cecil Textbook of Medicine. *Philadelphia: WB Saunders, 1988;18:329–337.*

2. Buja LM, Willerson JT. Clinicopathologic findings in 100 episodes of acute ischemic heart disease (acute myocardial infarction of coronary insufficiency) in 83 patients. *Am J Cardiol 1981;47:343–356.*

3. DeWood MA, Spores J, Notske R, Mouser LT, Burroughs R, Golden MS, Lang HT. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med 1980;303:897–902.*

4. Bush LR, Samowitz W, Buja LM, Rude RE, Willerson JT. Recovery of left ventricular segmental function after long-term reperfusion following temporary coronary occlusion in conscious dogs: comparison of 2- and 4-hour occlusions. *Circ Res 1983;53:248–263.*

5. Lavallee M, Cox D, Patrick TA, Vatner SF. Salvage of myocardial function by coronary artery reperfusion 1, 2 and 3 hours after occlusion in conscious dogs. *Circ Res 1983;53:235–247.*

6. Willerson JT, Scales F, Mukherjee A, Platt MR, Templeton GH, Fink GC, Buja LM. Abnormal myocardial fluid retention as an early manifestation of ischemic injury. *Am J Pathol 1977;87:159–188.*

7. Lang TW, Corday E, Gold H, Meerbaum S, Rubin S, Constantini C, Hirose S, Osher J, Rosen V. Consequences of reperfusion after coronary occlusion. Effects on hemodynamic and regional myocardial metabolic function. *Am J Cardiol 1974;33:69–81.*

8. Gaasch WH, Bing OHL, Pine MB, Franklin A, Clement J, Rhodes D, Phear WP, Weintraub RM. Myocardial contracture during prolonged ischemic arrest and reperfusion. *Am J Physiol 1979;235:H619–H627.*

9. Chien KR, Reeves JP, Buja LM, Bonte FJ, Parkey RW, Willerson JT. Phospholipid alterations in ischemic myocardium: temporal and topographical correlations with Tc-99m-PPi accumulation and an in vitro sarcolemmal Ca^{2+} permeability defect. *Circ Res 1981;48:711–719.*

10. Chien KR, Han A, Sen A, Buja LM, Willerson JT. Accumulation of unesterified arachidonic acid in ischemic canine myocardium: relationship to a phosphatidylcholine deacylation-reacylation cycle and the depletion of membrane phospholipids. *Circ Res 1984;54:313–322.*

11. Chien KR, Sen A, Reynolds R, Chang A. Kim Y, Gunn MD, Buja LM, Willerson JT. Release of arachidonate from membrane phospholipids in cultured myocardial cells during ATP depletion: correlation with the progression of cell injury. *J Clin Invest 1985;75:1770–1780.*

12. Mukherjee A, Wong TM, Templeton G, Buja LM, Willerson JT. Influence of volume dilution, lactate, phosphate and calcium on mitochondrial functions. *Am J Physiol 1979;237:224–238.*

13. Mukherjee A, Wong TM, Buja LM, Willerson JT. Oxidative phosphorylation in isolated canine myocardial mitochondria: effects of in vitro volume dilution, lactate, phosphate, and calcium addition, and lactic acidosis. In: Tajuddin M, Bhatia B, Siddiqui HH, Rona G, eds. Advances in Myocardiology. *Baltimore: University Park Press, 1988;2:339–347.*

14. Mukherjee A, Wong TM, Buja LM, Lefkowitz RJ, Willerson JT. Beta adrenergic and muscarinic cholinergic receptors in canine myocardium. Effects of myocardial ischemia. *J Clin Invest 1979;64:1423–1428.*

15. Mukherjee A, McCoy KE, Duke RJ, Hogan M, Hagler H, Buja LM, Willerson JT. Relationship between beta adrenergic receptor numbers and physiologic responses during experimental canine myocardial ischemia. *Circ Res 1982;50:735–741.*

16. Thandroyen FJ, Muntz K, Rosenbaum T, Ziman B, Willerson JT, Buja LM. Characterization of alterations of the beta adrenoreceptor-adenylate cyclase system during hypoxia in isolated cultured neonatal rat ventricular myocytes. *Am J Physiol 1989;256:H1204–H1217.*

17. Corr PB, Shayman JA, Kramer JB, Kipnis RJ. Increased alpha-adrenergic receptors in ischemic cat myocardium. A potential mediator of electrophysiological derangements. *J Clin Invest 1981;67:1232–1237.*

18. Sharma AD, Saffitz JE, Lee BI, Sobel BE. Alpha adrenergic-mediated accumulation of calcium in reperfused myocardium. *J Clin Invest 1983;72:802–818.*

19. Muntz KH, Hagler HK, Boulas JP, Willerson JT, Buja LM. Redistribution of catecholamines in the ischemic zone of the dog heart. *Am J Pathol 1984;114:64–78.*

20. Muntz KH, Olson EG, Lariviere GR, D'Souza S, Mukherjee A, Willerson JT, Buja LM. Autoradiographic characterization of beta adrenergic receptors in coronary blood vessels and myocytes in normal and ischemic myocardium of the canine heart. *J Clin Invest 1984;73:349–357.*

21. Reimer KA, Jennings RB. The "wavefront phenomenon" of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. *Lab Invest 1979;40:633–644.*

22. Bush LR. Buja LM, Tilton G, Wathen M, Apprill P, Ashton J, Willerson JT. Effects of propranolol and diltiazem alone and in combination on the recovery of left ventricular segmental function after long-term reperfusion following temporary coronary occlusion in conscious dogs. *Circulation 1985;72:413–430.*

23. Tilton GD, Bush LR, Apprill PG, Buja LM, Willerson JT. Effect of diltiazem and propranolol on left ventricular segmental relaxation during temporary coronary arterial occlusion and one month reperfusion in conscious dogs. *Circulation 1985;71:165–175.*

24. Sen A, Bunting S, Burton KP, Reynolds RC, Buja LM, Willerson JT, Chien KR. Inhibition of arachidonic acid release protects myocardial cell viability during ATP depletion. *J Clin Invest 1988;82:1333–1338.*

25. Burton KP. Evidence of direct toxic effects of free radicals on the myocardium. *Free Radic Biol Med 1988;41:15–24.*

26. Bolli R, Patel BS, Jerondi MO, Lai EK, McCay PB. Demonstration of free radical generation in "stunned" myocardium of intact dogs with the use of the spin trap alpha-phenyl N-test-butyl nitrone. *J Clin Invest 1988;82:476–485.*

27. Taylor AL, Golino P, Buja LM, Echols R. Is post-ischemic systolic dysfunction primarily caused by reperfusion? (abstr) *Circulation 1987;76:suppl IV:IV-228.*

28. Bush LR, Campbell WB, Tilton GD, Buja LM, Willerson JT. Effects of the selective thromboxane synthetase inhibitor dazoxiben on variations in cyclic blood flow in stenosed canine coronary arteries. *Circulation 1984;69:1161–1170.*

29. Bush LR, Campbell WB, Kern K, Tilton GD, Apprill P, Ashton J, Schmitz J, Buja LM, Willerson JT. The effects of alpha$_2$ adrenergic and serotonergic receptor blockade on platelet aggregation in stenosed canine coronary arteries. *Circ Res 1984;55:642–652.*

30. Apprill P, Schmitz JM, Campbell WB, Tilton G, Ashton J, Raheja S, Buja LM, Willerson JT. Cyclic blood flow variations induced by platelet activating factor in stenosed canine coronary arteries despite inhibition of thromboxane synthetase, serotonin receptors, and alpha-adrenergic receptors. *Circulation 1985;72:397–405.*

31. Ashton JH, Benedict CR, Fitzgerald C, Raheja S, Taylor A, Campbell W, Buja LM, Willerson JT. Serotonin is a mediator of cyclic flow variations in stenosed canine coronary arteries. *Circulation 1986;73:572–578.*

32. Ashton JH, Schmitz JM, Campbell WB, Ogletree ML, Raheja S, Taylor AL, Fitzgerald C, Buja LM, Willerson JT. Inhibition of cyclic flow variations in stenosed canine coronary arteries by thromboxane A_2/prostanglandin H_2 receptor antagonists. *Circ Res 1986;59:568–578.*

33. Ashton JH, Ogletree ML, Michel IM, Taylor AL, Raheja S, Schmitz J, Buja LM, Campbell WB, Willerson JT. Serotonin and thromboxane A_2/prostaglandin H_2 receptor activation cooperatively mediate cyclic flow variations in dogs with severe coronary artery stenoses. *Circulation 1987;76:952–959.*

34. Golino P, Ashton JH, Buja LM, Taylor AL, McNatt J, Rosolowsky M, Campbell WB, Willerson JT. Local platelet activation causes vasoconstriction of large epicardial canine coronary arteries in vivo: thromboxane A_2 and serotonin are possible mediators. *Circulation 1989;79:154–166.*

35. Willerson JT, Campbell WB, Winniford MD, Schmitz J, Apprill P, Firth B, Ashton J, Smitherman T, Bush L, Buja LM. Conversion from chronic to acute ischemic heart disease: speculation regarding mechanisms (editorial). *Am J Cardiol 1984;54:1349–1357.*

36. Willerson JT, Hillis LD, Winniford M, Buja LM. Speculation regarding mechanisms responsible for acute ischemic heart disease syndromes. *JACC 1986;8:245–250.*

37. Gold HK, Coller BS, Yasuda T, Saito T, Fallon JT, Guerrero JL, Leinbach RC, Ziskind AA, Collen D. Rapid and sustained coronary artery recanalization with combined bolus injection of recombinant tissue-type plasminogen activator and monoclonal antiplatelet GPIIb/IIIa antibody in a canine preparation. *Circulation 1988;77:670–677.*

38. Folts JD, Crowell EB Jr., Rowe GG. Platelet aggregation in partially obstructed vessels and its elimination with aspirin. *Circulation 1976;54:365–370.*

39. Golino P, Ashton JH, McNatt J, Glas-Greenwalt, P, O'Brien RA, Buja LM, Willerson JT. Simultaneous administration of thromboxane A_2 and serotonin S_2 receptor antagonists markedly enhances thrombolysis and prevents or delays

reocclusion after tissue-type plasminogen activator in a canine model of coronary thrombosis. *Circulation 1989;79:911–919.*

40. Golino P, Ashton JH, Glas-Greenwalt P, McNatt J, Buja LM, Willerson JT. Thromboxane A_2 and serotonin mediated reocclusion after thrombolysis with tissue-type plasminogen activator in a canine model of coronary thrombosis. *Circulation 1988;77:678–684.*

41. TIMI Research Group. Comparison of invasive and conservative strategies following intravenous tissue plasminogen activator in acute myocardial infarction: results of the thrombolysis in myocardial infarction (TIMI)II-B trial. *N Engl J Med 1989;320:618–627.*

42. Ryden L, Ariniego R, Arnman K. A double-blind trial of metoprolol in acute myocardial infarction: effects on ventricular tachyarrhythmias. *N Engl J Med 1983;308:614–618.*

43. Willerson JT, Muntz KH, Buja LM. Beta adrenergic antagonists after acute myocardial infarction: speculation concerning mechanisms responsible for their efficacy. *Houston Med J 1986;2:45–52.*

44. von der Lippe G, Schartum Hansen H, Lund-Johansen P, Nordrehaug JE, Haugen J, Eldjarn K, Hartmann A, Mellem H, Baekkevar M, Opedal I, Laszlo F, Hoist-Larsen L, Waage K, Heimdal K, Rod R, Fjosne U, Blystad L, Grebstad J, Endresen K, Foss PO, Wolff-Sorensen W, Disen A, Kvambe V, Hamre T, Tjorstad A, Heskestad A, Rodolen TR, Ytrehus K, Drivenes A, Torjussen T, Borovski G, Dehli O, Heldal M, Karoliussen O, Kannelonning KS, Seip TA, Johansen S, Fossli A, Dropping O, Bergh K, Dahl K, Tenstad O, Reksten R, Nordlie K, Noer H, Hagelund CH, Pedersen TR, Mangschau A, Berget K, Overskeid K, Gundersen T, Ronnevik PK, von Brandis C, Mikkelsen K, Barstad S, Skaland K, Abrahamsen AM, Nordahl E, Haugen L, Osnes G, Eide E, Fausa D, Wammer F, Frisvold OJ, Overskeid K, Abrahamsen AM, Frisvold OJ, Westlund K, Helle Berg S, Kjekshus J, Humerfelt SB, McFate Smith W, Robertson JIS, Hjort PF, Waaler HTh. The Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med 1981;304:801–807.*

45. Beta-Blocker Heart Attack Study Group. The beta-blocker heart attack trial. *JAMA 1981;246:2073–2074.*

46. Rude RE, Muller JE, Braunwald E. Efforts to limit the size of myocardial infarcts. *Ann Intern Med 1981;95:736–761.*

47. Serruys PW, Simoons ML, Suryapranata H, Vermeer F, Wijns W, Van den Brand M, Bar F, Zwaan C, Krauss XH, Remme WJ, Res J, Verheught FWA, Van Domburg R, Lubsen J, Hugenholtz PG. Preservation of global and regional left ventricular function after early thrombolysis in acute myocardial infarction. *JACC 1986;7:729–742.*

48. O'Rourke M, Baron D, Keogh A, Kelly R, Nelson G, Barnes C, Raftos J, Graham K, Hillman K, Newman H, Healey J, Woolridge J, Rivers J, White H, Whitlock R, Norris R. Limitation of myocardial infarction by early infusion of recombinant tissue-type plasminogen activator. *Circulation 1988;77:1311–1315.*

49. Rovelli F, DeVita C, Feruglio GA, Lotto A, Selvini A, Tognoni G, Farina ML, Foresti A, Franzosi MG, Mauri F, Pampallano S, Armitage P, Beria di Argentine A, Boeri R, Garrattini S, Mantegazza P, Menotti A, Peto R, Polli E, Verstraete M, Zanchetti A, Belli C, Binaghi G, Bossi M, Camerini F, Cristallo E, de Ambroggi L, Fazzini PF, Furlanello F, L'Abbate A, Milazzotto F, Piccolo E, Raviele A, Riggio G, Rossi P, Salerno JA, Santoboni A, Solinas P, Vecchio C, Zardini P, Donati MB, Manucci PM, Neri Serneri GG, Biraghi M, Chiuini E, Gasparini M, Maggioni AP, Pogna A, Volfi D, di Bitetto D, Colombo A, Masini C, Brusca A, Furlanello F, Bracchetti D, Ricciotti R, di Gregorio D, Correale E, Colonna L, Plastina F, Galassi A, Mereu D. Gruppo Italiano per lo Studio della streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocarcial infarcation. *Lancet 1986;1:397–402.*

Arrhythmias and Mortality in Congestive Heart Failure

John Kjekshus, MD

The extent and severity of myocardial dysfunction and risk of dying are associated with the occurrence of ventricular arrhythmias. However, there is a dissociation between the frequency of ventricular arrhythmias and the prevalence of sudden death among patients with congestive heart failure. Sudden death occurs in 8 to 10% of New York Heart Association functional class I patients and in 20% of class II, III and IV patients, despite increased frequency of malignant arrhythmias and functional deterioration. Yearly mortality rates increase from 12 to 15% in class I and II and is 60% in class IV. Sudden death in class I and II is 50 to 60% of all deaths, whereas in class IV it amounts to only 20 to 30%. The most important cause of death in class IV is progressive congestive heart failure.

Ventricular arrhythmia is a trigger event in the development of fatal arrhythmia which depends on a substrate of myocardial scar tissue, hypertrophy and aberrant conducting pathways. However, regional myocardial ischemia, transmembrane electrolyte differences and myocardial stores of catecholamines are important modulators. Depletion of myocardial catecholamines and down-regulation of myocardial β-adrenergic receptors in the myocardium may explain tolerance to ventricular tachyarrhythmias observed in patients with severe congestive heart failure and intolerance to conventional antiarrhythmic drugs.

Although angiotensin-converting enzyme (ACE) inhibitors may reduce ventricular arrhythmias, the important role of ACE inhibitors in severe congestive heart failure is to prevent progression of myocardial dysfunction and congestive heart failure. To date, however, ACE inhibitors have not been demonstrated to have a significant effect on the incidence of sudden death. This does not preclude an effect on fatal arrhythmias among patients with milder heart failure and intact stores of myocardial catecholamines.

(Am J Cardiol 1990;65:42 I–48 I)

From the Department of Medicine, Bærum Hospital, Sandvika, Norway.

Address for reprints: John Kjekshus, MD, Department of Medicine, Bærum Hospital, Sandvika—1316, Norway.

Patients with chronic congestive heart failure have a high incidence of ventricular arrhythmia and sudden death.[1–11] It is generally assumed that ventricular arrhythmia may degenerate to ventricular fibrillation, the fatal arrhythmia in most patients who die suddenly.[10–14] Patients with frequent arrhythmias usually have extensive coronary artery disease which is often associated with recent myocardial infarction, hypertrophy and dysfunction.[15–19] The extent of myocardial dysfunction is clearly related to overall mortality and cardiac death.[20] The prevalence of malignant arrhythmias, especially nonsustained ventricular tachycardia (VT), is also related to the extent of myocardial dysfunction. Functional derangement of patients is associated with increased nonsustained VT, as revealed by 24-hour electrocardiogram, in less than 10% of patients in New York Heart Association functional class I to 70% among class IV patients (Fig. 1).[2–4,7,9,20–22] The question remains, however, whether there is an independent role of ventricular ectopic activity as a determinant for sudden death or if it is incidental to the myocardial dysfunction.

ARRHYTHMIAS IN CONGESTIVE HEART FAILURE

The trigger event to VT is assumed to be reentrant activity, or enhanced automaticity, induced by a substrate of arrhythmogenic myocardium (Table I). This involves extensive scarring, dilatation and hypertrophy of the myocardium. The occasional degeneration of arrhythmias to ventricular fibrillation may be modulated by severe myocardial ischemia or by loss of autonomic control with increased neurohormonal activation and loss of inhibitory vagal activity.[23,24] An increase in myocardial wall tension and heart rate frequently observed in congestive heart failure may contribute to regional myocardial ischemia, resulting in marked dispersion of the membrane potential which may further enhance electrical instability. Electrolyte disturbances, especially hypokalemia and hypomagnesemia, are caused by elevation of circulating catecholamines, angiotensin and aldosterone, and from use of diuretics and digitalis and are associated with increased occurrence of ventricular fibrillation. In addition, catecholamines increase the automaticity of Purkinje fibers by increasing the slope of phase 4 depolarization. Therapy with antiarrhythmic drugs, digitalis, β-adrenergic agonists and phosphodiesterase inhibitors may be arrhythmogenic by enhanced triggering of ectopic activity or subsequently to their depressant effect on the myocardium (i.e., these drugs may be arrhythmogenic either directly, by precipitating ventricular dilata-

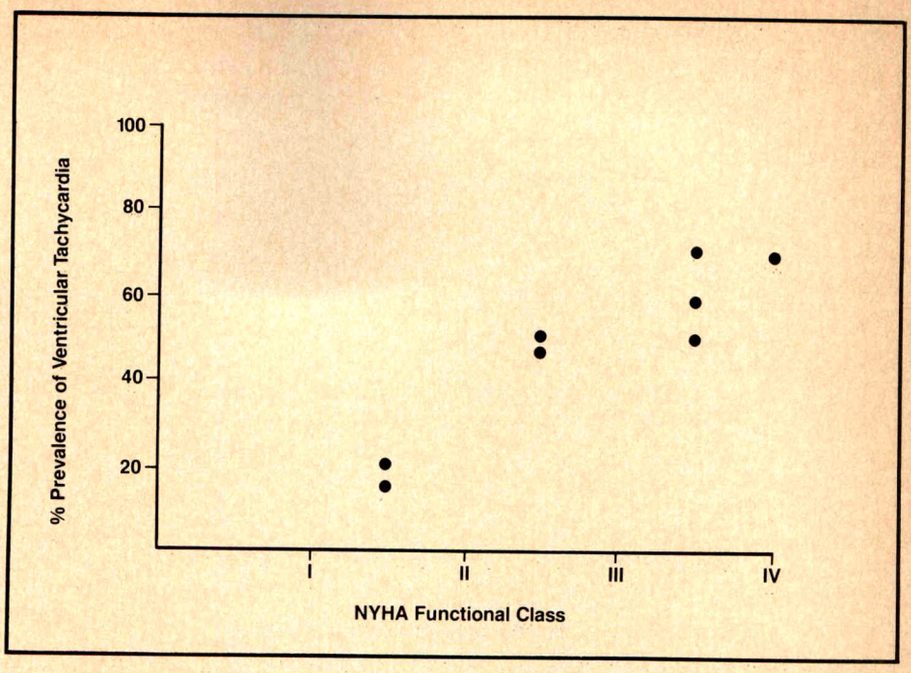


FIGURE 1. The relationship between New York Heart Association (NYHA) functional class and the prevalence of nonsustained ventricular tachycardia adapted from 8 different studies.[2–4,7,9,20–22]

tion, or secondarily to the chronotropic and inotropic effects that may aggravate the myocardial oxygen demand/supply ratio).

MODE OF DEATH IN CONGESTIVE HEART FAILURE

The major causes of death in congestive heart failure are sudden death and death from progressive heart failure. More infrequent causes of death are myocardial rupture, asystole, stroke and death from noncardiac origins (Table II). Sudden death is assumed to be death resulting from cardiac arrhythmia. Sudden death, defined as unexpected death within 1 hour after onset of symptoms, is presaged by arrhythmias in 90% of all such events.[10] Ventricular fibrillation was the terminal rhythm in 81% of cases of sudden death[13] and was preceded by VT in most patients. The occurrence of malignant arrhythmias, especially VT, has been assumed to be instrumental in precipitating sudden death. Therefore, VT has been assumed to be of prognostic importance and accordingly should be treated to prevent sudden death.[25,26]

The association between VT and death is probably independent of etiology. Ikegawa et al[27] showed that in patients with idiopathic cardiomyopathy the incidence of sudden death was highly predictable when occurrence of nonsustained VT and frequent ventricular premature complexes (VPCs) of more than 100/hour were combined. Bigger et al[26] demonstrated that nonsustained VT had marked effects on survival and on arrhythmic death among patients after infarction. However, the 92 patients with VT were sicker than the 728 without VT. Yet, when adjustments were made for recorded differences in risk variables, the presence of VT nearly doubled the risk of dying within a 31-month follow-up period. Other important risk variables may have been operative as well. Episodes of silent ischemia, neurohormonal activation, extent of myocardial dysfunction and hypertrophy were not

TABLE I Arrhythmias and Sudden Death in Congestive Heart Failure

Triggering activities
Reentrant activity
Enhanced automaticity
Delayed after potentials
Myocardial substrates
Scar tissue
Aneurysm
Hypertrophy
Ventricular dilatation
Ventricular dysfunction
Modulating events
Myocardial ischemia
Electrolyte deficits
Myocardial release of cathecholamines
Sympatoadrenergic activation
Myocardial stretch
Antiarrhythmic drugs
Inotropic drugs
Diuretics

TABLE II Mode of Death in Congestive Heart Failure

Sudden death (<1 hour)
Ventricular fibrillation
Progressive myocardial failure
Asystole
Secondary ventricular fibrillation
Recurrent myocardial infarction
Other circulatory disorders
Myocardial rupture
Stroke
Pulmonary embolism
Noncardiac cause

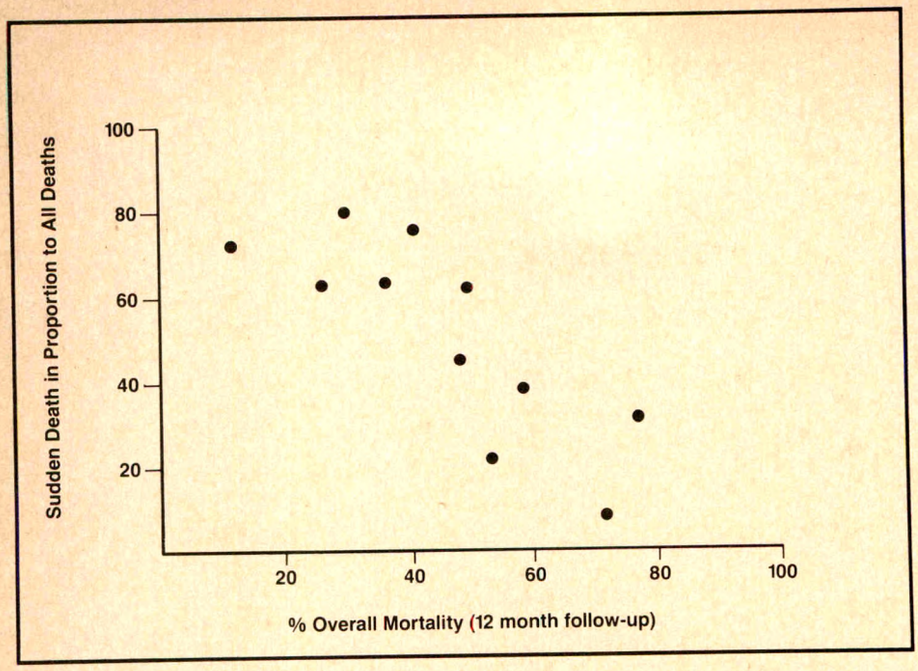


FIGURE 2. The proportion of all deaths caused by sudden death according to 1-year mortality among patients in New York Heart Association (NYHA) class I to IV adapted from 11 different studies.[1–11]

determined in this study and may have accounted for observed differences between groups.

Congestive heart failure appears to be an ill-defined heterogenous syndrome and mode of death seems to differ according to different expressions of the syndrome. Total mortality among patients with mild heart failure is low. However, the proportion of patients dying suddenly is large; 50 to 70% of all deaths are sudden in class I and II.[1–11] Serious arrhythmias are relatively infrequent among these patients. The occurrence of malignant arrhythmia increases with the severity of the myocardial dysfunction (Fig. 1). Patients in class III and IV have an overall yearly mortality of 40 to 60%. The proportion of patients dying suddenly, relative to all deaths, amounts to less than 30% (Fig. 2). The major cause of death in severe congestive heart failure (class III and IV) is from progressive deterioration of myocardial function, whereas the rate of sudden death remains comparable to that in class II and accounts for 10 to 30% of all patients irrespective of functional class (Fig. 3). Analysis of arrhythmias and mode of death reported in studies of congestive heart failure according to functional class therefore suggests no clear association between occurrence of ventricular arrhythmias and sudden, presumably, arrhythmic death.

ARRHYTHMIC DEATH AND NEUROHORMONAL ACTIVITY

Patients with severe congestive heart failure have high levels of circulating catecholamines that are closely related to a poor prognosis.[24,28,29] Increased neurosympathetic stimulation down-regulates myocardial β receptors,[30] and myocardial catecholamine stores are markedly depleted[31] because of reduced reuptake of released catecholamines.[32] Experiments in dogs have shown that ventricular fibrillation occurs when myocardial ischemia is coupled with sympathetic nervous stimulation of the myocardium and catecholamine excess from the myocardium. After severing the stellate ganglion, the myocardium became tolerant to the same ischemia, and ventricular arrhythmias were no longer inducible.[33] Depletion of catecholamine stores by reserpine prevented ventricular fibrillation during experimental coronary occlusion. The dissociation between frequently occurring ventricular tachyarrhythmias and the relatively low prevalence of sudden death in severe congestive heart failure may be related to depletion of myocardial catecholamine stores and consequent blunting of the modulating effect on trigger events.

ARRHYTHMIC DEATH AND MYOCARDIAL ISCHEMIA

Lack of neurohormonal control is associated with a high risk of dying among patients with myocardial dysfunction.[29] This is reflected in monotonous tachycardia with very low variation in beat-to-beat RR interval. Regional myocardial ischemia and release of myocardial catecholamines together with loss of vagal control may therefore have an important enhancing effect on the triggering activity. Recordings of 24-hour electrocardiograms, obtained in patients dying suddenly, have shown that immediate precursors of sudden death, in addition to frequent ventricular ectopic activity, was ST-segment deviation before ventricular fibrillation.[34] Frank myocardial infarction may be the initiating event that caused arrhythmias; however, coagulation myocytolysis necrosis is found in 71% of the patients dying suddenly.[35,36] This finding is typically associated with states of excessive catecholamine excretion. The autopsy findings of Davies and Thomas[37] showed that 74% of the patients who died

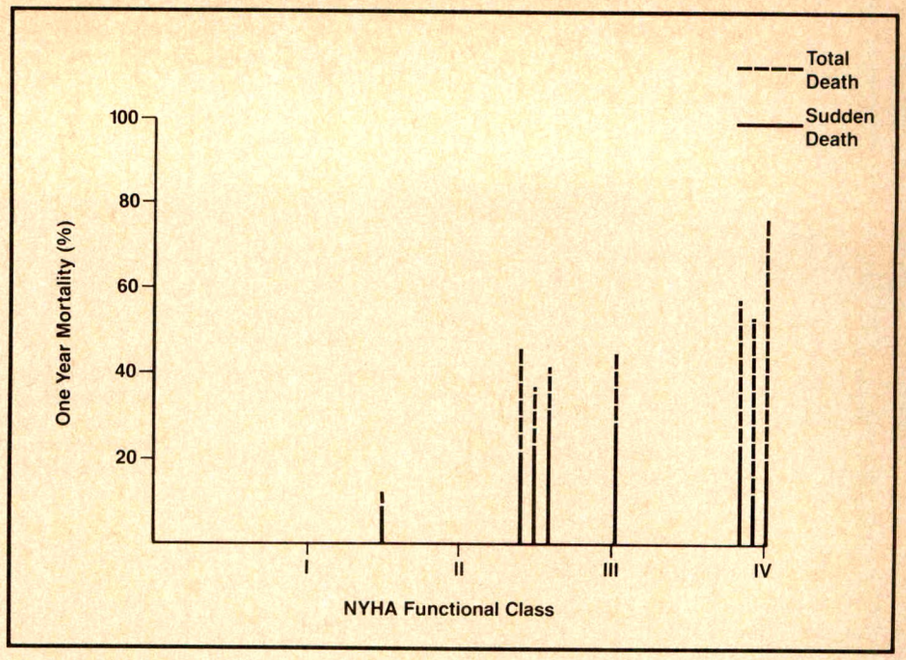


FIGURE 3. Prevalence of total (*broken line*) and sudden death (*solid line*) by New York Heart Association (NYHA) functional class and 1-year mortality adapted from 6 different studies.[1,2,4,6,9,11]

unexpectedly, i.e., within 6 hours, had subocclusive intraluminal thrombi; 20% had plaque fissures and very few, 5%, did not have occlusive lesions. This finding lends support to the importance of episodes of regional ischemia and catecholamine release as a contributing mechanism.

ARRHYTHMIC DEATH AND INTERVENTION

Recent information from the Cardiac Arrhythmia Suppression Trial, a prospective double-blind, randomized trial, suggested that conventional antiarrhythmic drugs may actually increase mortality among patients in mild to moderate heart failure after acute myocardial infarction.[38,39] Generally, information from studies on mild to moderate heart failure is not applicable to patients with severe heart failure. Class IV patients have not been studied with respect to the effect of antiarrhythmic treatment on mortality because of their overall low tolerance to conventional antiarrhythmic drugs. A trend toward increasing mortality with milrinone suggests that inotropic drugs may be harmful as well.[40] In contrast, β-receptor antagonists that block sympathetic stimulation of the myocardium have been shown to reduce mortality and sudden death, specifically, during and after acute myocardial infarction.[6,41] This effect is not associated with an effect on ventricular tachyarrhythmias.[41] Protection by β blockade is not restricted to patients with coronary disease; similar results are suggested by studies in patients with dilated cardiomyopathy without coronary artery disease.[42] Prevention of myocardial ischemia by reducing heart rate seems to be instrumental in prolonging survival.[43] Experience from coronary surgery suggests that prevention of ischemia by revascularization of main stem lesions prevents death within 24 hours after onset of symptoms.[44]

It has been suggested that reduction of myocardial pre- and afterload by nitrates and angiotensin-converting enzyme (ACE) inhibitors, which improves myocardial residual flow, can reduce ventricular arrhythmias in patients with mild to moderate heart failure.[45–47] Only 1 mortality study has been performed with vasodilators among patients with severe congestive heart failure who are prone to frequent arrhythmias.[9] The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) studied patients with severe heart failure (New York Heart Association class IV). Patients (n = 253) were randomized to treatment with placebo and the ACE inhibitor enalapril. One-year mortality among patients taking placebo was 52% and among those taking enalapril 36%. The major cause of death in the CONSENSUS was progressive heart failure. Treatment effects were accounted for by the subset of patients for which prevention of progressive deterioration of heart failure was obtained (Fig. 4). Patients who died unexpectedly, within 1 hour after onset of symptoms, accounted for 20% of all deaths and no treatment effect could be documented with this subset (Fig. 5). This latter observation is at variance with previous studies of patients with moderate heart failure demonstrating a reduction of ventricular ectopic activity with ACE inhibitors.[45–47] The differential effect of enalapril on progressive heart failure and sudden death was consistent among patients with myocardial dysfunction caused by ischemic as well as nonischemic heart disease.[9,48] The subset of patients dying suddenly was small, and it may be argued that classification of death may be influenced by the effect of enalapril on the clinical condition. However, death was blindly classified by 2 independent investigators.

A subset of patients in the CONSENSUS were examined with 24-hour electrocardiographic analyses at base-

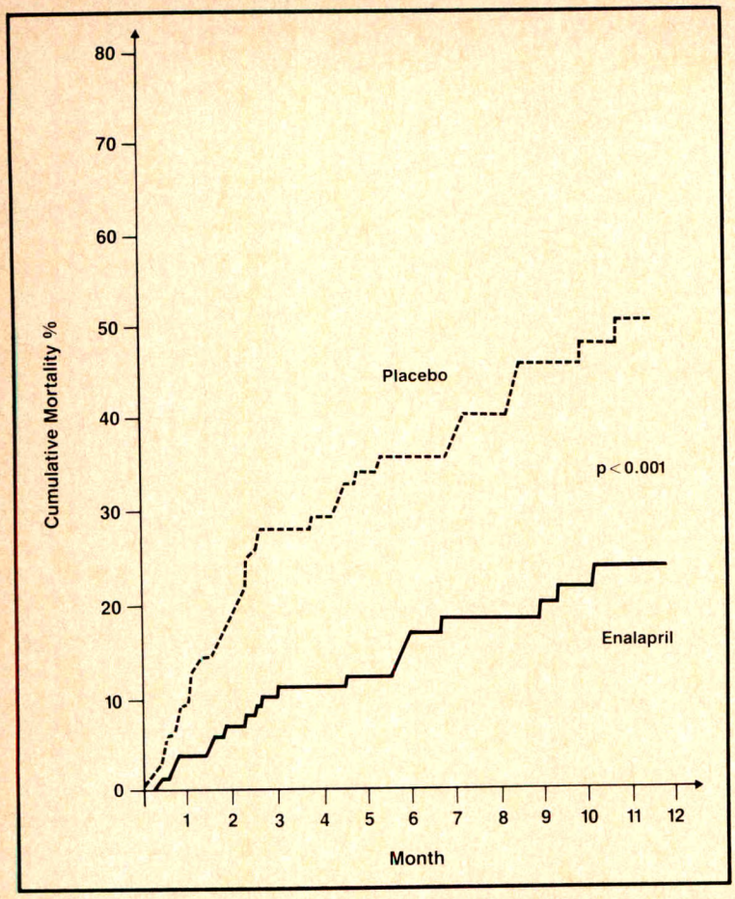


FIGURE 4. Mortality due to progression of congestive heart failure–intention to treat analysis in the Cooperative North Scandinavian Enalapril Survival Study. (Adapted with permission from *Am J Cardiol.*[48])

line and after 6 weeks of treatment. All patients had frequent VPCs, averaging 200 to 300 VPCs/hour. There was no difference between survivors and deceased with respect to ectopic activity. Seventy percent of all the patients had nonsustained VT at baseline. No difference in the rate of subsequent 6-month mortality was observed irrespective of whether VT was present or not. Reduction in ventricular ectopic activity was not related to change in mortality or mode of death.

All patients were examined with respect to neurohormonal activation at baseline and at 6 weeks. In general, catecholamines, angiotensin, aldosterone and atrial natri-

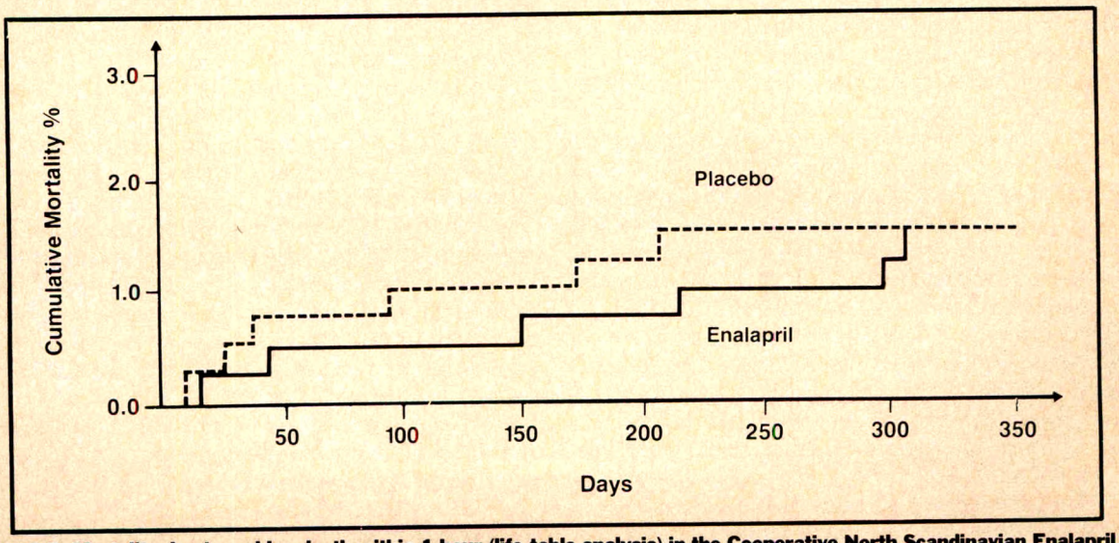


FIGURE 5. Mortality due to sudden death within 1 hour (life-table analysis) in the Cooperative North Scandinavian Enalapril Survival Study. (Adapted with permission from *Am J Cardiol.*[48])

uretic peptide (ANP) were greatly elevated. Neurohormonal activation was variable in all patients; however, no relationship was found between catecholamines, angiotensin II or aldosterone and the occurrence of ventricular VPCs or VT.

In contrast, ANP was related to occurrence of VT. ANP released after increased stretch of the atria reflected increased left ventricular filling pressures. Patients with VPCs combined with runs of VT had higher ANP concentrations than patients with VPCs alone. This suggests that VT is dependent on myocardial dysfunction and may explain the association between VT and prognosis.[15]

Enalapril effectively reduced ANP after 6 weeks of treatment, whereas ANP in the placebo group remained unchanged.[29] The reduction in ANP may reflect a reduction in filling pressure and improved hemodynamic conditions during administration of enalapril and may explain the reduction of arrhythmias observed with ACE inhibitors.[45,46]

Lack of relationship between changes in norepinephrine, angiotensin, aldosterone and ventricular arrhythmias does not preclude the importance of myocardial neurohormonal activation as a mechanism for fatal arrhythmias. Down-regulation of myocardial β receptor and depletion of myocardial catecholamine stores in these patients may confer relative protection against arrhythmias.

The neurohormones are important predictors of death in congestive heart failure.[29] By combining the neurohormones at baseline, a predictive score was derived that defined a 6-month mortality of 20% among nonactivators to almost 100% among patients with the largest neurohormonal activation.[29] These scores identified a group of high activators with marked effect of enalapril on overall mortality and a group of low activators without documented effect of enalapril on mortality. Patients who died from progressive heart failure were almost exclusively among high activators, whereas sudden death was evenly distributed among high and low activators. High circulating hormonal activity in this study is therefore not a predictor of increased susceptibility to sudden death, but may predict death from progression of congestive heart failure. The level of circulating hormonal activity also identified patients who benefited from ACE inhibitor treatment. Reduced stores of myocardial catecholamines or blocking of β receptors may be clinically important in blunting the modulating effect of sympathetic stimulation on ventricular arrhythmias.

CONCLUSION

The extent of myocardial dysfunction is associated with increased occurrence of malignant arrhythmias, yet in severe congestive heart failure, death is generally caused by progression of congestive heart failure and not sudden death. Sudden death is more often observed among asymptomatic or less symptomatic patients. It is unclear whether ACE inhibitors reduce arrhythmias in congestive heart failure, and so far ACE inhibition has only been demonstrated to cause fewer deaths from progressive congestive heart failure, not sudden death.

REFERENCES

1. Franciosa JA, Wilen M, Ziesche S, Cohn JN. Survival in men with severe chronic left ventricular failure due to either coronary heart disease or idiopathic dilated cardiomyopathy. *Am J Cardiol 1983;51:832–836.*

2. Wilson JR, Schwartz S, St John Sutton M, Ferraro N, Horowitz LN, Reichek N, Josephson ME. Prognosis in severe heart failure: relation to hemodynamic measurements and ventricular ectopic activity. *JACC 1983;2:403–410.*

3. Meinertz T. Hofmann T, Kasper W, Treese N, Bechtold H, Stienin U, Pop T, von Leithner E, Andresen D, Meyer J. Significance of ventricular arrhythmias in idiopathic dilated cardiomyopathy. *Am J Cardiol 1984;53:902–907.*

4. Chakko CS, Gheorghiade M. Ventricular arrhythmias in severe heart failure: incidence, significance and effectiveness of antiarrhythmic therapy. *Am Heart J 1985;109:497–504.*

5. Hinkle L. The immediate antecedents of sudden death. *Acta Med Scand 1981;210:suppl 681:207–217.*

6. Lund-Johansen P. The Norwegian Multicenter Study on Timolol after myocardial infarction. Part II. Effect in different risk groups, causes of death, heart arrest, reinfarctions, rehospitalizations and adverse experiences. *Acta Med Scand 1981;210:suppl 681:243–252.*

7. Maskin CS, Siskind SJ, LeJemtel TH. High prevalence of nonsustained ventricular tachycardia in severe congestive heart failure. *Am Heart J 1984;107:896–901.*

8. Cleland JGF, Dargie HJ, Ford I. Mortality in heart failure: clinical variables of prognostic value. *Br Heart J 1987;58:572–582.*

9. The CONSENSUS trial study group. Effects of enalapril on mortality in severe congestive heart failure. *N Engl J Med 1987;316:1429–1435.*

10. Goldstein S, Friedman L, Hutchinson R, Canner P, Romhilt D, Schlant R, Sobrino R, Verter J, Wasserman A, Aspirin myocardial infarction study group. Timing, mechanism and clinical setting of witnessed deaths in postmyocardial infarction patients. *JACC 1984;3:1111–1117.*

11. Lee WH, Packer M. Prognostic importance of serum sodium concentration and its modification by converting enzyme inhibition in patients with severe chronic heart failure. *Circulation 1986;73:257–267.*

12. Savage HR, Kissane JQ, Becher EL, Maddocks WQ, Murtaugh JT, Dizadji H. Analysis of ambulatory electrocardiograms in 14 patients who experienced sudden death during monitoring. *Clin Cardiol 1987;10:621–632.*

13. Nicolic G, Bishop RL, Singh JB. Sudden death recorded during Holter monitoring. *Circulation 1982;66:218–225.*

14. Kempf FC, Josephson ME. Cardiac arrest recorded on ambulatory electrocardiogram. *Am J Cardiol 1984;53:1577–1582.*

15. The Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. *N Engl J Med 1983;309:331–336.*

16. McLennachan JM, Henderson E, Morris KI, Dargie HJ. Ventricular arrhythmias in patients with hypertensive left ventricular hypertrophy. *N Engl J Med 1987;317:787–792.*

17. Kreger BE, Cupples A, Kannel WB. The electrocardiogram in prediction of sudden death: Framingham study experience. *Am Heart J 1987;113:377–382.*

18. Messerli FH, Ventura HO, Elizardi DJ, Dunn FG, Frohlich ED. Hypertension and sudden death. *Am J Med 1984;77:18–22.*

19. Norris RM, Barnaby PF, Brandt PWT, Geary GG, Whitlock RM, Wild CJ, Barratt-Boyes BG. Prognosis after recovery from first acute myocardial infarction: determinants of reinfarction and sudden death. *Am J Cardiol 1984;53:408–413.*

20. Rocco MB, Sherman H, Cook EF, Weisberg M, Flatley M, Goldman L. Correlates of cardiac and sudden death after ambulatory monitoring in a community hospital. *J Chron Dis 1987;40:977–984.*

21. Huang SK, Messer JV, Denes P. Significance of ventricular tachycardia in idiopathic dilated cardiomyopathy: observations in 35 patients. *Am J Cardiol 1983;51:507–512.*

22. Lichstein E, Morganroth J, Harrist R, Hubble E, BHAT study group. Effect of propranolol on ventricular arrhythmias. The Beta-Blocker–Heart Attack Trial Experience. *Circulation 1983;67:suppl I:I-5–I-10.*

23. Eckberg DL, Drabinsky M, Braunwald E. Defective cardiac parasympathetic control in patients with heart disease. *N Engl J Med 1971;285:877–883.*

24. Francis G. Neuroendocrine manifestations of congestive heart failure. *Am J Cardiol 1988;62:9A–13A.*

25. Bigger JT. Why patients with congestive heart failure die: arrhythmias and sudden cardiac death. *Circulation 1987;75:28–35.*

26. Bigger JT, Fleiss JL, Rolnitzky LM, Multicenter postinfarction research group. Prevalence, characteristics and significance of ventricular tachycardia detected by 24-hour continuous electrocardiographic recordings in the late hospital phase of acute myocardial infarction. *Am J Cardiol 1986;58:1151–1160.*

27. Ikegawa T, Chino M, Hasegawa H, Usaba F, Suzuki S, Ookura M, Mishihawa K. Prognostic significance of 24 hour ambulatory electrocardiographic monitoring in patients with dilative cardiomyopathy: a prospective study. *Clin Cardiol 1987;10:78–82.*

28. Cohn JN, Levine TB, Olivari MT. Plasma norepinephrine as a guide to

prognosis in patients with chronic congestive heart failure. *N Engl J Med 1984;311:819–823.*

29. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. *Circulation; in press.*

30. Bristow MR, Ginsburg R, Minobe W, Cubicciotti RS, Sageman WR, Billingham M, Stinson E, Harrison DC. Decreased catecholamine sensitivity and beta-adrenergic receptor density in failing human hearts. *N Engl J Med 1982;307:205–211.*

31. Chidsey CA, Braunwald E, Morrow AG, Mason DT. Myocardial norepinephrine concentration in man: effects of reserpine and congestive heart failure. *N Engl J Med 1963;269:653–658.*

32. Henderson EB, Kahn JK, Corbett JR, Hansen DE, Pippin JJ, Kulkarni P, Ugolini V, Akers MS, Hansen CHR, Buja LM, Parkey RW, Willerson JT. Abnormal I-123 metaiodobenzylguanidine myocardial washout and distribution may reflect myocardial adrenergic derangement in patients with congestive cardiomyopathy. *Circulation 1988;78:1192–1199.*

33. Schwartz PJ, Billman GE, Stone HL. Autonomic mechanisms in ventricular fibrillation induced by myocardial ischemia during exercise in dogs with healed myocardial infarction. An experimental preparation for sudden cardiac death. *Circulation 1984;69:790–800.*

34. Gottlieb SO, Gottlieb SH, Achuff SC, Baumgardner R, Mellitsa ED, Weisfeldt ML, Gerstenblith G. Silent ischemia on Holter-monitoring predicts mortality in high-risk postinfarction patients. *JAMA 1988;259:1030–1035.*

35. Baroldi G, Falzi G, Mariani F. Sudden coronary death. A post mortem study in 208 selected cases compared to 97 "control subjects." *Am Heart J 1979;98:20–27.*

36. Baroldi G. Different morphological types of myocardial cell death in man. Recent advances in studies on cardiac structure and metabolism. In: Fleckenstein A, Rona G, eds. Pathophysiology and Morphology of Myocardial Cell Alteration. *Baltimore, London, Tokyo: University Park Press, 1975;16:383–397.*

37. Davies MJJ, Thomas A. Thrombosis and acute coronary-artery lesions in sudden cardiac ischemic death. *N Engl J Med 1984;310:1137–1140.*

38. The Cardiac Arrhythmia Suppression Trial investigators preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia. Suppression after myocardial infarction. *N Engl J Med 1989;321:406–412.*

39. Stewart RA, McKenna WJ, Poloniecki JD, Michelson JK, Das SK, Morady F, Shork MA, Pitt B, Niclas JM. Prospective, randomized, double blind, placebo controlled trial of low dose amiodarone in patients with severe heart failure and frequent ventricular ectopy (abstr). *Eur Heart J 1989;10:229.*

40. DiBianco R, Shabetai R, Kostuk W, Moran J, Schlant RC, Wright R. A comparison of oral milorinone, digoxine and their combinations in the treatment of patients with chronic heart failure. *N Engl J Med 1989;320:677–683.*

41. Ryden L, Arimego R, Arneman K, Herlitz J, Hjalmarson Å, Holmberg S, Reyes C, Smedgård P, Swedberg K, Vedin A, Waagstein F, Waldenstrøm A, Wilhelmsson C, Wedel H, Yamamoto M. A double-blind trial of metoprolol in acute myocardial infarction. *N Engl J Med 1983;308:614–618.*

42. Swedberg K, Hjalmarson Å, Waagstein F, Wallentin I. Prolongation of survival in congestive cardiomyopathy by beta-receptor blockade. *Lancet 1979; 1:1374–1376.*

43. Kjekshus J. Importance of heart rate in determining beta blocker efficacy in acute and long term acute myocardial infarction intervention trials. *Am J Cardiol 1986;57:43F–49F.*

44. Holmes DR, Davis KB, Mock MB, Fisher LD, Gersh BJ, Killip T, Pettinger M, and Participants in the Coronary Artery Surgery Study. The effect of medical and surgical treatment on subsequent sudden cardiac death in patients with coronary artery disease: a report from the Coronary Artery Surgery Study. *Circulation 1986;73:1254–1263.*

45. Webster MWI, Fitzpatrick A, Nicholls G, Ikram H, Wells E. Effects of enalapril on ventricular arrhythmias in congestive heart failure. *Am J Cardiol 1985;56:566–569.*

46. Cleland JGF, Dargie HJ, Hodsman GP, Ball SG, Robertson JIS, Morton JJ, East BW, Robertson I, Murray GD, Gillen G. Captopril in heart failure. A double blind controlled trial. *Br Heart J 1984;52:530–535.*

47. Dennick LG, Masin CS, Meyer JH, Schotz WE, Brown BW. Enalapril for congestive heart failure. *N Engl J Med 1987;137:1349–1350.*

48. Swedberg K, Kjekshus J. The CONSENSUS Trial Study Group. Effect of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *Am J Cardiol 1988;62:60A–66A.*

Renal Protective Effects of Angiotensin-Converting Enzyme Inhibition

William F. Keane, MD, and Bruce E. Shapiro, MD

Nephron loss is a common progression of a diverse range of kidney diseases. Recent experimental models of chronic renal disease have suggested that hemodynamic and nonhemodynamic mechanisms play key roles in progressive renal injury. Extensive renal ablation in the rat was followed by development of altered glomerular hemodynamics. Albuminuria and histologic damage leading to focal glomerulosclerosis were preceded by the development of increased glomerular pressures and were prevented by interventions such as severe dietary protein restriction and angiotensin-converting enzyme (ACE) inhibitor therapy. Both experimental interventions ameliorated glomerular hypertension. It was therefore concluded that these interventions ameliorated injury by glomerular hemodynamic effect. Similar findings were obtained in a rat model of type I diabetes mellitus induced by streptozotocin in which glomerular hemodynamic factors appeared important to the development of progressive renal disease. Recent studies have suggested that nonhemodynamic factors have important roles in the progression of glomerular injury. For example, although the predominant effects of ACE inhibitor therapy appear to be hemodynamically mediated, data are emerging which suggest that these agents may also influence growth/proliferation of glomerular cells. Because hyperplasia/hypertrophy may influence glomerular susceptibility to injury, this may also be a potential mechanism whereby ACE inhibitor therapy influences glomerular damage. In addition, a variety of studies have suggested that hyperlipidemia, which is a frequent accompaniment of glomerular disease, is an important modulator of glomerular injury independent of glomerular hemodynamic effects. Coagulation factors, calcium phosphorus balance, as well as the genetic susceptibility of the glomerulus to injury, all appear to contribute to progressive nephron destruction.

(Am J Cardiol 1990;65:49 I–53 I)

From the Division of Nephrology, Department of Medicine, Hennepin County Medical Center, University of Minnesota Medical School, Minneapolis, Minnesota.

Address for reprints: William F. Keane, MD, Hennepin County Medical Center, 710 Park Avenue South, Minneapolis, Minnesota 55415.

Clinical studies of angiotensin-converting enzyme (ACE) inhibitor therapy in renal disease, although preliminary, have demonstrated the antihypertensive efficacy of these agents. ACE inhibitor therapy produces only modest changes in glomerular filtration rate while increasing renal plasma flow. Most studies of nondiabetic patients with renal disease have shown a reduction in protein excretion after ACE inhibitor treatment, whereas studies in diabetics have shown a more varied response of proteinuria during ACE inhibitor treatment. Preliminary, uncontrolled studies have suggested that ACE inhibitor therapy may alter the rate of progression of renal disease, and well controlled studies in diabetic and nondiabetic patients with renal disease have now been initiated.

It is relatively well established that once a critical number of nephrons are destroyed by disease, renal function will decline even in clinical situations in which the original cause of injury has resolved. Factors, such as severity of disease, uncontrolled hypertension, obstruction and renal parenchymal infection have long been recognized as contributing to the progression of renal disease. However, recent investigations have indicated that a variety of other factors may also influence the rate of progression of end-stage renal failure. These factors, which are often a consequence of a reduced nephron population, may also participate in injuring the remaining nephrons. It has been proposed that the adaptive changes in glomerular hemodynamics, e.g., increased glomerular pressure that occurs in remaining functioning nephrons may play a critical role in the progression of renal disease.[1] Importantly, nonhemodynamic factors have also been identified as contributing to glomerular injury. For example, hyperlipidemia, which is a frequent abnormality in progressive renal insufficiency, has been experimentally shown to be a risk factor for progressive glomerular damage independent of glomerular hemodynamics. It has been postulated that progressive glomerular injury may have similar risk factors as has been proposed in large vessel atherosclerotic injury. A better understanding of the factors that contribute to progressive renal disease is underscored by the 30,000 new patients requiring treatment, as well as by the 3.5 billion dollar yearly expenditure needed for the care of patients with end-stage renal disease.

GLOMERULAR HEMODYNAMIC ALTERATIONS AND THE PROGRESSION OF RENAL DISEASE

Experimental models of renal disease have been developed in an attempt to clarify the factors involved in progressive decline of renal function. The most extensively

TABLE I Interventions Shown to Ameliorate Progressive Renal Injury in the Renal Ablation Model of Progressive Renal Insufficiency

Dietary Modification
Protein restriction
Phosphate restriction
Carbohydrate (energy) restriction
Polyunsaturated fatty acid supplementation
Exercise
Antihypertensive agents
Enalapril (angiotensin-converting enzyme inhibitor)
Verapamil (calcium channel blocker)
Lipid lowering agents
Clofibrate
Lovastatin
Thromboxane synthetase inhibitor
Anticoagulants
Heparin
Coumadin

studied is the rat remnant kidney model. In this model, renal insufficiency is induced by unilateral nephrectomy and infarction of two-thirds of the remaining kidney. Soon after this ablative procedure, remaining nephrons hypertrophy and glomerular capillary flow and hydraulic pressure increases. Systemic hypertension, proteinuria, and histologically, focal segmental glomerulosclerosis predictably develop over a period of 2 to 3 months. Progressive azotemia and eventual death of the animal ensues.[1–8] A critical factor in progressive glomerular destruction appears to be the hemodynamic change within the glomerulus induced by the loss of renal mass, specifically, glomerular hypertension.[3] Under normal circumstances, the glomerular capillary bed is protected from systemic hypertension by increases in afferent arteriolar resistance. However, in the setting of reduced nephrons and in an attempt to compensate for their loss, afferent arteriolar resistance decreases, thereby increasing single nephron plasma flow rate. Systemic hypertension may then be transmitted to the glomerulus, resulting in glomerular hypertension and ultimately glomerular damage and functional loss.

In the remnant kidney model, seemingly unrelated interventions have been observed to attenuate glomerular injury, with a corresponding decline in the rate of disease progression (Table I). One such intervention is dietary protein restriction, which reduces compensatory glomerular hypertrophy and decreases glomerular plasma flow rate. Although the development of systemic hypertension is not affected by this maneuver, glomerular capillary pressures remain normal and the development of proteinuria and glomerular injury are blunted.[3,9]

Recent studies have been performed using antihypertensive therapy aimed at reducing systemic pressure. In these studies, enalapril was compared with conventional hypertensives ("triple therapy") consisting of reserpine, hydralazine and hydrochlorothiazide. Despite similar reductions in blood pressure, only in enalapril-treated rats was urinary protein excretion dramatically reduced, reflecting amelioration of glomerular damage. Survival was also prolonged in rats treated with ACE inhibitors.[10–16] This effect was seen in the absence of major alterations in glomerular filtration or plasma flow rates, although glomerular pressure was dramatically reduced. These data suggested that glomerular hypertension was a primary factor responsible for development of progressive glomerular injury. Despite adequate control of systemic hypertension in rats treated with "triple therapy," there was no reduction in glomerular pressures nor alteration in the course of their progressive renal disease.[14] The disparity between the actions of ACE inhibitors and other classes of antihypertensives in the reduction of glomerular hypertension appeared to hinge on the ability of the ACE inhibitor to lower efferent arteriolar resistance, a property that appeared unique to ACE inhibitors compared with other classes of antihypertensive agents.[17–20]

In addition to preventing the development of glomerular disease in the renal ablation model, both protein restriction and ACE inhibitor therapy have been shown to reduce the rate of progression of established disease.[9,11] In these studies, both enalapril and protein restriction limited glomerular capillary pressure and retarded glomerular injury even when therapy was delayed until systemic hypertension, proteinuria and glomerulosclerosis were well established.

Glomerular hemodynamic changes appeared to play a key role in the development of renal disease in an experimental model of type I diabetes mellitus. Insulin-dependent diabetes was induced by streptozotocin, and rats so treated subsequently developed characteristic morphologic glomerular changes, including hypertrophy, basement membrane thickening, hyaline deposition and glomerulosclerosis.[21,22] Studies of glomerular hemodynamics, soon after establishment of diabetes, have demonstrated increased glomerular filtration rate and flows.[23] In some studies, an increased glomerular capillary pressure has been noted.[23,24] In these diabetic rats, albuminuria gradually increased and glomerulosclerosis became evident over a 14-month interval. Functional glomerular and morphologic changes occurred in the absence of systemic hypertension. When enalapril was administered to these normotensive diabetic rats, in doses that produced a reduction of systemic blood pressure by 15 to 20 mm Hg, a selective decrease in glomerular capillary pressure was observed.[23,24] Proteinuria was reduced and the development of glomerulosclerosis was prevented.[23,24] The effect of enalapril on glomerular capillary pressure was the result of a significant reduction in efferent arteriolar resistance.

NONHEMODYNAMIC FACTORS INVOLVED IN THE PROGRESSION OF RENAL DISEASE

Other experimental studies of renal disease have suggested that hemodynamic factors are not the sole cause of progressive glomerular injury. This was initially suggested by studies using anticoagulants.[25] Specifically, heparin was shown to reduce the incidence of glomerulosclerosis in the renal ablation model without affecting glomerular hemodynamics.[26] This effect was probably not a result of heparin's anticoagulant properties, because low molecular weight heparin, which is devoid of anticoagulant ef-

TABLE II Effect of Angiotensin-Converting Enzyme Inhibitors in Type I Diabetes Mellitus

Study	No. of Pts.	Duration (mo)	MAP Initial (mm Hg)	MAP Δ (%)	GFR Initial (ml/min)	GFR Δ (%)	Albuminuria Initial (mg/24 hour)	Albuminuria Δ (%)
Mimran[37]	8	1.5	95	−5*	149	−6	123	−41*
Marre[38]	10	6	100	−10*	130	+8*	120	−69*
Hommel[39]	16	3	112	−9*	99	−6*	1,589	−32*
Passa[40]	10	12	124	−15	72	+15	50	−76
Morelli[42]	13	3	98	−8*	63	0	1,096	−30
Bjork[43]	14	24	120	−5*	37	−30*	2,900	−3

* Statistically different from baseline.
GFR = glomerular filtration rate; MAP = mean arterial pressure; Δ = change.

fects, also reduced glomerular injury in rats with renal ablation.[27] The precise mechanism whereby heparin molecules reduce glomerular injury is unknown, but heparin is known to have cell growth inhibitory properties in a variety of in vitro settings. Specifically, heparin has been shown to inhibit glomerular mesangial cell growth in a dose-dependent fashion.[28]

Therapy with lipid-lowering agents also appears to have a significant impact on the progression of renal disease. In the renal ablation model, therapy with clofibric acid or lovastatin effectively decreased hyperlipidemia.[29] Importantly, these therapies dramatically reduced proteinuria and the incidence of glomerulosclerosis independent of changes in systemic blood pressure or glomerular hemodynamics.[29] These antilipemic agents have been also used in the obese Zucker rat, a model of type II diabetes mellitus with hyperlipidemia and progressive glomerular disease.[30–33] In this model, neither systemic nor glomerular hypertension appeared to participate in the development of glomerular injury.[30,31] Moreover, reduction in circulating cholesterol was associated with a decrease in albuminuria and preservation of glomerular structure.[32] These beneficial effects occurred without affecting systemic blood pressure or glomerular hemodynamics.[32]

The possibility that inhibition of ACE might be associated with other nonhemodynamic effects was recently suggested by studies in a model of persistent nephrotic syndrome induced by the aminonucleoside of puromycin.[34] In these studies, amelioration of glomerular injury by captopril occurred without reduction in glomerular capillary pressure.[34] More recently, studies in obese Zucker rats have suggested a nonhemodynamic effect of ACE inhibitors. Obese Zucker rats treated with enalapril for 8 months had a significant reduction in albuminuria.[35] Importantly, the progressive increase in cholesterol levels that parallels albuminuria were not observed.[35] Morphologically, a fivefold reduction in the extent of glomerular injury was also found. Although systemic blood pressure was normal, it was reduced by 10 to 15 mm Hg; no change in glomerular capillary pressure was observed. Renal and glomerular growth was significantly less in enalapril-treated obese Zucker rats.[35] These studies further suggested a nonhemodynamic benefit from ACE inhibitor therapy. The mechanism of these effects is not understood, but may be related to an effect of angiotensin II on renal tubular and glomerular cell growth.[36] In summary, experimental results suggest that ACE inhibitors may exert their renal effects through hemodynamic as well as nonhemodynamic mechanisms.

CLINICAL STUDIES OF THE USE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS IN PATIENTS WITH RENAL DISEASE

Experience with the use of ACE inhibitors in human renal disease is expanding rapidly. There are no completed double-blind, randomized, controlled trials comparing these agents with conventional antihypertensive agents in patients with renal impairment. Promising results suggested by experimental studies, previously outlined, have instigated a number of trials investigating the effects of ACE inhibitor therapy in human renal disease. In diabetic patients (Table II) with persistent microalbuminuria,

TABLE III Effects of Angiotensin-Converting Enzyme Inhibitors on Systemic Blood Pressure, Renal Function and Proteinuria in Patients with Nondiabetic Chronic Renal Insufficiency

Study	No. of Pts.	Months of Treatment	Drug	Blood Pressure Response	Proteinuria	GFR	RBF	FF
Cooper[51]	41	12	E	⇓	NR	NR	NR	NR
Reams[45]	9	1	E	⇓	⇓	↔	⇑	⇓
Heeg[46]	13	3	L	⇓	⇓	⇓	⇓	⇓
Bauer[47]	23	36	E	⇓	NR	⇑	⇑	↔
Heeg[52]	7	2	L	⇓	⇓	⇑	⇑	⇓
Ruilope[53]	10	12	C	⇓	⇔	⇑	⇑	⇔

C = captopril; E = enalapril; FF = fillration fraction; GFR = glomerular fillration rate; L = lisinopril; NR = not recorded; RBF = renal blood flow; ⇑ = increase; ⇓ = decrease; ↔ = no change.

normal glomerular function and normal blood pressure, captopril slightly reduced systemic blood pressure.[37,38] This result was associated with a decline in albuminuria and an increase in glomerular filtration rate (GFR) and renal plasma flow. In slightly hypertensive diabetic patients with incipient nephropathy, ACE inhibitor therapy administered over a 12-week period significantly decreased blood pressure and decreased albuminuria by 30%, whereas GFR decreased slightly from 99 to 92 ml/min/1.73 m^2.[39]

In established diabetic nephropathy, treatment with ACE inhibitors produced a variable effect on proteinuria.[39–44] In 1985, Taguma et al[41] reported a 50% reduction in urinary protein excretion in 10 patients with heavy proteinuria treated for 8 weeks with an ACE inhibitor. Other investigators, however, have reported no significant change in protein excretion rates during ACE inhibitor therapy in clinical diabetic nephropathy.[42,43] In a reported study of hypertensive type II diabetics with renal disease, captopril reduced systemic blood pressure without significantly changing GFR or renal plasma flow. Proteinuria was reduced by nearly 25%, but this was not statistically significant.[44]

When ACE inhibitor therapy has been instituted in nondiabetic patients with chronic renal disease (Table III), reductions in proteinuria (−50%) have been reported both in short-term studies and in long-term evaluations.[45–52] However, not all patients with proteinuria had reductions in protein excretion rates during ACE inhibitor therapy. Recent studies have suggested that the sodium status of the patient is critical to the effect on proteinuria; i.e., the reduction of proteinuria seen with ACE inhibitor therapy can be abrogated by a high sodium diet.[52]

In nondiabetic patients with renal disease, ACE inhibitor alone or in combination with other antihypertensive agents effectively reduces blood pressure with minimal change in renal function (Table III). When measured, GFR remained unchanged or decreased slightly, while renal plasma flow remained constant or increased. Few long-term studies (>6 months) have been performed, but reports suggest that similar renal hemodynamic changes are seen with prolonged ACE inhibitor therapy.[45,53,54]

CONCLUSIONS

Despite considerable interest sparked by the demonstrated renal protective effects of ACE inhibitor experimental models, its potential in human renal disease is unknown. Few long-term studies have been completed and results thus far are preliminary. Although 1 study in diabetic patients reported a significant reduction in the rate of decline of renal function, a control group was not included.[43] In nondiabetic patients, slowing of progressive renal disease has also been shown, although these studies were not prospective control trials. Thus, although these preliminary observations are encouraging, prospective trials currently underway may clarify this important question. Nevertheless, the weight of the experimental and clinical data suggests that this class of antihypertensive agents has important implications for the treatment of patients with renal disease.

REFERENCES

1. Brenner BM. Nephron adaptation to renal injury or ablation. *Am J Physiol 249:F324–F337.*

2. Meyer TW, Rennke HG. Progressive glomerular injury after limited renal infarction in the rat. *Am J Physiol 1988;254:F856–F862.*

3. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA. Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *Am J Physiol 1981;241:F85–F93.*

4. Kaufman JM, Siegel NJ, Hayslett JP. Functional and hemodynamic adaptation to progressive renal ablation. *Circ Res 1975;36:286–293.*

5. Deen WM, Maddox DA, Robertson CR, Brenner BM. Dynamics of glomerular ultrafiltration in the rat. VII. Response to reduced renal mass. *Am J Physiol 1974;227:556–562.*

6. Purkerson ML, Hoffsten PE, Klahr S. Pathogenesis of the glomerulopathy associated with renal infarction in rats. *Kidney Int 1976;9:407–417.*

7. Allison MEM, Lipham EM, Lassiter WE, Gottschalk CW. The acutely reduced kidney. *Kidney Int 1973;3:354–363.*

8. Yoshida Y, Fogo A, Shiraga H, Glick AD, Ichikawa I. Serial micropuncture analysis of single nephron function in subtotal renal ablation. *Kidney Int 1988;33:855–867.*

9. Nath KA, Kren SM, Hostetter TH. Dietary protein restriction and established renal injury in the rat. Selective role of glomerular capillary pressure and progressive glomerular dysfunction. *J Clin Invest 1986;78:1199–1205.*

10. Anderson S, Meyer TW, Rennke HG, Brenner BM. Control of glomerular hypertension limits glomerular injury in rats with reduced renal mass. *J Clin Invest 1985;76:612–619.*

11. Meyer W, Anderson S, Rennke HG, Brenner BM. Reversing glomerular hypertension stabilizes established glomerular injury. *Kidney Int 1987;31:752–759.*

12. Raij L, Chiou XC, Owens R, Wrigley B. Therapeutic implications of hypertension: induced glomerular injury. *Am J Med 1985;79:suppl 3C:37–41.*

13. Jackson B, Johnston CI. The contribution of systemic hypertension to progression of chronic renal failure in the rat remnant kidney: effect of treatment with an angiotensin converting enzyme inhibitor or a calcium inhibitor. *J Hypertens 1988;6:495–501.*

14. Anderson S, Rennke HG, Brenner BM. Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. *J Clin Invest 1986;77:1993–1205.*

15. Hall RL, Wilke WL, Fettman MJ. Captopril slows the progression of chronic renal disease in partially nephrectomized rats. *Toxicol Appl Pharmacol 1985; 80:517–526.*

16. Jackson B, Whitty M, Debrevi L, Cubela R. Preservation of renal structure and function in the rat remnant kidney model of chronic renal failure by enalapril treatment. *Pathology 1987;19:38–42.*

17. Pelayo JC, Harris DCH, Schrier RW. Glomerular hemodynamic adaptations in remnant nephrons: effect of verapamil. *Am J Physiol 1988;254:F425–F431.*

18. Frei U, Schindler R, Graf S, Koch KM. Glomerular hemodynamics of the clipped kidney: effects of calcium antagonist and converting enzyme inhibition (abstr). *Proc Xth Int Cong Nephrol, 1987:277.*

19. Anderson S, Clarey LE, Riley SL, Troy JL. Acute infusion of calcium channel blockers reduces glomerular capillary pressure in rats with reduced renal mass (abstr). *Kidney Int 1988;33:370.*

20. Dworkin LD, Benstein J, Feiner HD, Parker M. Nifedipine prevents glomerular injury without reducing glomerular pressure in rats with desoxycorticosterone salt hypertension (abstr). *Kidney Int 1988;33:374.*

21. Mauer SM, Michael AF, Fish AJ, Brown DM. Spontaneous immunoglobulin and complement deposition in glomerular diabetic rats. *Lab Invest 1972;27:488–494.*

22. Rasch R. Studies on the prevention of glomerulopathy in diabetic rats. *Acta Endocrinol 1981;suppl 242:43–44.*

23. Zatz R, Meyer TW, Rennke HG, Brenner BM. Predominance of hemodynamic rather than metabolic factors in the pathogenesis of diabetic glomerulopathy. *Proc Natl Acad Sci USA 1985;82:5963–5967.*

24. Zatz R, Dunn BR, Meyer TW, Anderson S, Rennke HG, Brenner BM. Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. *J Clin Invest 1986;77:1925–1930.*

25. Klahr S, Heifets M, Purkerson ML. The influence of anticoagulation on the progression of experimental renal disease. In: Mitch WE, Brenner BM, Stein JH, eds. The Progressive Nature of Renal Disease. *New York: Churchill Livingstone, 1986:45–64.*

26. Ichikawa I, Yoshida Y, Fogo A, Purkerson ML, Klahr S. Effect of heparin on the glomerular structure and function of remnant nephrons. *Kidney Int 1988; 34:638–644.*

27. Purkerson ML, Tollefson BM, Klahr S. N-desulfated-acetylated heparin ameliorates the progression of renal disease in rats with subtotal renal ablation. *J Clin Invest 1988;81:69–74.*

28. Castellano JJ, Hoover RL, Harper RA, Karnovsky MJ. Heparin and glomer-

ular epithelial cell-secreted heparin-like species inhibit mesangial cell proliferation. *Am J Pathol 1985;120:427–435.*
29. Kasiske BL, O'Donnell MP, Garvis WJ, Keane WF. Pharmacological treatment of hyperlipidemia reduces glomerular injury in rat 5/6 nephrectomy model of chronic renal failure. *Circ Res 1988;62:367–374.*
30. Kasiske BL, Cleary MP, O'Donnell MP, Keane WF. Effects of genetic obesity on renal structure and function in the Zucker rat. *J Lab Clin Med 1985;106:598–604.*
31. O'Donnell MP, Kasiske BL, Cleary MP, Keane WF. Effects of genetic obesity on renal structure and function in the Zucker rat. II. Micropuncture studies. *J Lab Clin Med 1985;106:605–610.*
32. Kasiske BL, O'Donnell MP, Cleary MP, Keane WF. Treatment of hyperlipidemia reduces glomerular injury in obese Zucker rats. *Kidney Int 1988;33:667–672.*
33. Kasiske BL, O'Donnell MP, Keane WF. The obese Zucker rat model of glomerular injury in type II diabetes. *J Diabetic Complications 1987;1:26–29.*
34. Fogo A, Yoshida Y, Glick AD, Homma T, Ichikawa I. Serial micropuncture analysis of glomerular function in two rat models of glomerulosclerosis. *J Clin Invest 1988;82:322–330.*
35. O'Donnell MP, Kasiske BL, Schmitz PG, Katz SA, Keane WF. Enalapril reduces glomerular injury in obese Zucker rats (abstr). *Kidney Int 1989;35:434.*
36. Yoshida Y, Fogo A, Ichikawa I. Glomerular hypertrophy has a greater impact on glomerular sclerosis than the adaptive hyperfunction in remnant nephrons (abstr). *Kidney Int 1988;33:327.*
37. Mimran A, Insua A, Ribstein J, Monnier L, Bringer J, Mirouze J. Contrasting effects of captopril and nifedipine in normotensive patients with incipient diabetic nephropathy. *J Hypertens 1988;6:919–923.*
38. Marre M, LeBlanc H, Suarez L, Guyenne TT, Menard J, Passa P. Converting enzyme inhibition and kidney function in normotensive diabetic patients with persistent microalbuminuria. *Br Med J 1987;294:1448–1452.*
39. Hommel E, Parving HH, Mathiesen E, Edsberg B. Effect of ACE-In on kidney function in insulin dependent diabetic patients with nephropathy. *Br Med J 1986;293:467–470.*
40. Passa P, LeBlanc H, Marre M. Effects of enalapril in insulin-dependent diabetic subjects with mild to moderate uncomplicated hypertension. *Diabetes Care 1987;10:200–204.*
41. Taguma Y, Kitamoto Y, Futaki G, Ueda H, Monma H, Ishizaki M, Takahashi H, Sekino H, Sasaki Y. Effect of ACE-In on heavy proteinuria in azotemic diabetics. *N Engl J Med 1985;313:1617–1620.*
42. Morelli E, Loon NR, Myers BD. Effect of converting enzyme inhibitor on diabetic glomerular injury (abstr). *Kidney Int 1989;35:211.*
43. Bjork S, Nyberg G, Mulec H, Granerus G, Herlitz H, Aurell M. Beneficial effects of angiotensin converting enzyme inhibition on renal function in patients with diabetic nephropathy. *Br Med J 1986;293:467–470.*
44. Valvo E, Bedogna V, Casagrande P, Antiga L, Zamboni M. Captopril in patients with type II diabetes and renal insufficiency: systemic and renal hemodynamic alterations. *Am J Med 1988;85:344–348.*
45. Reams GP, Bauer JH. Effect of enalapril in subjects with hypertension associated with moderate to severe renal dysfunction. *Arch Intern Med 1986;146:2145–2148.*
46. Heeg JE, DeJong PE, Van Der Hem GK, de Zeeuw D. Reduction of proteinuria by angiotensin converting enzyme inhibition. *Kidney Int 1987;32:78–83.*
47. Bauer JH, Reams GP, Sunder ML. Renal protective effect of strict blood pressure control with enalapril therapy. *Arch Int Med 1987;147:1397–1400.*
48. Abraham PA, Opsahl JA, Halstenson CE, Keane WF. Efficacy and renal effects of enalapril therapy for hypertensive patients with chronic renal insufficiency. *Arch Intern Med 1988;148:2358–2362.*
49. Lagrue G, Robeva R, Laurent J. Antiproteinuric effect of captopril in primary glomerular disease. *Nephron 1987;46:99–100.*
50. Keane WF, Anderson S, Aurell M, de Zeeuw D, Narins RG, Povar G. Angiotensin converting enzyme inhibitors and progressive renal insufficiency: current experience and future directions. *Ann Intern Med 1989;111:503.*
51. Cooper WD, Doyle G, Donohoe J, Laher M, Ledingham J, Raine A, Melnick SC, Unsworth J, Raman V, Vandenburg A, Wollard M. Enalapril in the treatment of hypertension associated with impaired renal function. *Br J Clin Pharmacol 1985;20:280–281.*
52. Heeg JE, deJong PE, Van der Hem, de Zeeuw D. Antiproteinuric effect of the ACE-inhibitor lisinopril (abstr). *Kidney Int 1989;35:227.*
53. Ruilope LM, Miranda B, Morales JM, Rodicio JL, Romero JC, Raij L. Converting enzyme inhibition in chronic renal failure. *Am J Kidney Dis 1989;2:120–126.*
54. Maschio G, Rugiu OL. Long-term clinical effects of enalapril on progression of chronic renal failure (abstr). *Kidney Int 1988;33:379.*

Vol 65/21

The American Journal of Cardiology

M. 1. 91

JUNE 4, 1990

A Symposium: Advances in Nitrate Therapy (Part 2)

CALCUTTA UNIVERSITY CENTRAL LIBRARY

GUEST EDITORS:

Adam Schneeweiss, MD
Director, Cardiovascular Research Foundation
Geneva, Switzerland

Marija Weiss, DSc
Director, International Medical Affairs
Schwarz Pharma AG
Monheim, Federal Republic of Germany

A YORKE MEDICAL JOURNAL/CAHNERS PUBLISHING COMPANY

The American Journal of Cardiology

JUNE 4, 1990 VOL. 65 NO. 21

A Symposium: Advances in Nitrate Therapy (Part 2)

GUEST EDITORS:

Adam Schneeweiss, MD
Director, Cardiovascular Research Foundation
Geneva, Switzerland

Marija Weiss, DSc
Director, International Medical Affairs
Schwarz Pharma AG
Monheim, Federal Republic of Germany

This symposium was held in Montreux, Switzerland (as part of the Cardiovascular Therapy Forum meeting). This supplement contains presentations from the symposium and related topics, and was supported by educational grants from C.V.R.F. and Schwarz Pharma.

EDITOR IN CHIEF
William C. Roberts, MD

MANAGING EDITOR, SPECIAL PROJECTS
Judith Wagner

PUBLISHER, SPECIAL PROJECTS
Kenton T. Finch

PRODUCTION EDITOR
Joan Gunning

PROOF EDITOR
Mary Crowell

THE AMERICAN JOURNAL OF CARDIOLOGY.® (ISSN 0002-9149) June 4, 1990, Vol. 65, No. 21 (USPS: 505–750).

Member, American Business Press, Inc. and Audit Bureau of Circulations. Published 4 times in January, February, March, May, June, July, September and October, 3 times in April, August and November, and 2 times in December, by The Cahners Publishing Company, a Division of Reed Publishing USA, 275 Washington St., Newton, MA 02158-1630. Terrence M. McDermott, President; Jerry D. Neth, Vice President/Publishing Operations; J.J. Walsh, Financial Vice President/Magazine Division; Thomas J. Dellamaria, Vice President/Production and Manufacturing.

SUBSCRIPTIONS: Solicited only from cardiologists and other physicians. Publisher reserves the right to refuse unqualified subscribers. Subscribers agree that no article or any part thereof published in any editions of the American Journal of Cardiology received under this subscription agreement may be copied, recorded or reproduced in any form or by any means, electronic or mechanical, including, among other things, photocopying or the storing of part or all of such articles on any information retrieval system, without the written permission of the Publisher. Address correspondence regarding subscriptions and changes of address to: THE AMERICAN JOURNAL OF CARDIOLOGY, 44 Cook Street, Denver, Colorado 80206-5800 (1-800-637-6073). Please include your zip code and, in case of change of address, copy of old address label. Changes of address must reach the Journal one month preceding month of issue. Single copy price: Regular issues $10.00; Symposium and special issues $12.00. Subscription rate for individuals in field of publication: United States 1 year $66, 2 years $112, 3 years $158; Canada and all other countries 1 year $105, 2 years $178, 3 years $252; Residents and Medical Students: United States 1 year $33; Canada & all other countries 1 year $85. Institutions: United States 1 year $95, 2 years $162, 3 years $228; Canada & all other countries 1 year $125, 2 years $213, 3 years $300. Air Mail available at additional charge of $150 per year. The Journal is not responsible for replacing missing issues unless the Circulation Department is notified of nonreceipt within 3 months of issue date.

Second class postage paid at Denver, CO, and at additional mailing office. Printed in U.S.A. Trademark™ in U.S. Patent Office. © Copyright 1990 by Reed Publishing USA: Saul Goldweitz, Chairman; Ronald G. Segel, President and Chief Executive Officer. All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording or by any information storage retrieval system, without permission of the copyright owner. Prices on bulk reprints of articles available on request.

The Publisher assumes no liability for any material published in the Journal. All statements are the responsibility of the authors.

MANUSCRIPTS: Address all manuscripts to William C. Roberts, MD, Editor-in-Chief, the American Journal of Cardiology, 7960 Old Georgetown Road, Suite 2C, Bethesda, Maryland 20814.

POSTMASTER: Send address changes to: The American Journal of Cardiology, 44 Cook Street, Denver, Colorado 80206-5800.

Cahners Publishing Company, A Division of Reed Publishing USA □ Specialized Business Magazines for Building & Construction □ Manufacturing □ Foodservice & Lodging □ Electronics & Computers □ Interior Design □ Printing □ Publishing □ Industrial Research & Technology □ Health Care □ Entertainment.

CALCUTTA CENTRAL LIBRARY

CONTENTS

The American Journal of Cardiology

JUNE 4, 1990 VOL. 65 NO. 21

A SYMPOSIUM:
ADVANCES IN NITRATE THERAPY (PART 2)

1J
Introduction
Adam Schneeweiss and Marija Weiss

2J
Individualized Antianginal Therapy Guided by Systemic Arterial Pressure
Adam Schneeweiss and Leonardo Reisin

6J
Evaluation of the Efficacy and Duration of Action of Isosorbide Mononitrate in Angina Pectoris
Mark A. de Belder, Adam Schneeweiss, and A. John Camm

9J
Long-Term Efficacy of Nitroglycerin Patch in Stable Angina Pectoris
Raffaele Greco, Mario Schiattarella, Simona Wolff, Doriana D'Alterio, and Pio Tartaglia

16J
Interval Treatment of Coronary Artery Disease with Sustained-Release Isosorbide-5-Mononitrate
Wolfgang Jansen, Regina Prenze, Hartmut Kümper, and Michael Tauchert

23J
Nitrate Therapy in the Elderly
Joseph S. Alpert

28J
Nitrate Tolerance in Heart Failure: Differential Venous, Pulmonary and Systemic Arterial Effects
Nabeel Makhoul, Nader Dakak, Moshe Y. Flugelman, Amnon Merdler, Arie Shefer, Adam Schneeweiss, David A. Halon, and Basil S. Lewis

32J
Efficacy of Isosorbide-5-Mononitrate on Painful and Silent Myocardial Ischemia After Myocardial Infarction
Jianzhang Feng, Xiu-Hua Feng, and Adam Schneeweiss

36J
Prevention of Creatine Kinase-MB Release in Coronary Artery Disease and Pacing-Induced Myocardial Ischemia by Isosorbide Dinitrate Spray
Alon Marmor and Robert Klein

39J
A Dose-Finding Study of the Hemodynamic Effect of Isosorbide Dinitrate Spray in Congestive Heart Failure
Robert Klein and Tali Sharir

43J
Comparative Evaluation of a New Formulation of Isosorbide Dinitrate Oral Spray and Sublingual Nitroglycerin Tablets
Alon Marmor

46J
Randomized Double-Blind Comparison of Isosorbide Dinitrate and Nifedipine in Variant Angina Pectoris
Michael Aschermann, Jan Bultas, Debora Karetová, Frantisèk Kölbel, Michaela Kozáková, and David Simper

50J
Intravenous Isosorbide-5-Mononitrate in the Treatment of Acute Myocardial Infarction
Dženana E. Rezaković, Vladimir Goldner, Zdravko Batinić, Marija Weiss, Janez Štalec, and Leo Pavičić

Publisher's Note

The opinions expressed in this presentation are those of the panelists and are not attributable to the sponsor or the publisher, editor, or editorial board of The American Journal of Cardiology. Clinical judgment must guide each physician in weighing the benefits of treatment against the risk of toxicity. References made in the articles may indicate uses of drugs at dosages, for periods of time, and in combinations not included in the current prescribing information.

Editor's suggestion: The symposium issues for a full year should be bound together separately from the regular issues.

The American Journal of Cardiology

Introduction

Adam Schneeweiss, MD, and Marija Weiss, DSc

A decade of extensive research in cardiovascular therapy has threatened the important position of nitrates in the field. In ischemic heart disease the development of new calcium antagonists provided new effective drugs that were expected to reduce the rate of reinfarction and postinfarction deaths, rapidly relieve chest pain in angina pectoris and effectively prevent anginal episodes. Ultrashort-acting β blockers have been developed for use in some of the conditions in which intravenous nitrates are used. In heart failure, the angiotensin-converting enzyme (ACE) inhibitors were shown to produce hemodynamic and clinical improvement and to reduce mortality, thereby gaining a leading position in therapy. In reviewing published reports, it was found that there were almost 10 times the amount of studies on calcium antagonists or ACE inhibitors than on nitrates.

When this huge amount of data is carefully analyzed, nitrates stand very well in the efficacy competition. Sublingual nitrates are still the most rapid way of relieving pain in angina pectoris and improving hemodynamics in heart failure. Moreover, new nitrate spray formulations, acting even more rapidly then sublingual tablets, are now available. Their efficacy in prevention of anginal episodes is at least comparable to that of other antianginal drugs. Intravenous nitrates are still first-line drugs for use in patients with unstable angina in the coronary care unit. The use of ultrashort-acting β blockers is still very limited and the indications for their use are fewer than those for nitrates.

Some of the great early expectations from calcium antagonists have not been fulfilled. Their greatest failure is in secondary prevention after acute myocardial infarction (except for diltiazem in non-Q-wave infarction).

Isosorbide dinitrate combined with hydralazine was the first drug that reduced mortality in patients with chronic congestive heart failure of various functional classes.

ACE inhibitors are very promising in heart failure, but the data supporting their use are limited to a study with enalapril in patients in New York Heart Association Class IV and to a study with captopril in a relatively small number of patients. The ongoing Veterans Administration Vasodilator Heart Failure Trial 2 compares the effect of isosorbide dinitrate and hydralazine to that of an ACE inhibitor on mortality in chronic heart failure. The results are not yet available.

The issue of tolerance is still raising concern for some aspects of nitrate therapy. However, it is clear that "smart" use of nitrates, i.e., low doses, asymmetric regimens and a dose-free interval, can largely prevent tolerance.

This symposium reports on the advances in nitrate therapy presented in international meetings in 1989 and highlights certain points investigated but not presented previously.

Individualized Antianginal Therapy Guided by Systemic Arterial Pressure

Adam Schneeweiss, MD, and Leonardo Reisin, MD

Antianginal and antihypertensive treatment are closely related. All drugs used for treatment of angina pectoris are effective also in the treatment of hypertension. This is certainly true for drugs such as β-adrenoreceptor blockers and calcium antagonists, which are considered first-line antihypertensive drugs. Even nitrates are effective in certain forms of hypertension, such as isolated systolic hypertension in the elderly. Drugs that have been developed purely for treatment of hypertension, such as the angiotensin-converting enzyme inhibitors are now evaluated for treatment of angina pectoris, with variable results. Even α-adrenoreceptor blockers such as prazosin were found effective in certain forms of angina pectoris.

CAUSES FOR THE OVERLAP IN TREATMENT

The pathophysiology of angina pectoris and hypertension and the mechanisms of treatment contribute to the overlap between the 2 therapeutic indications.

Chronic stable angina pectoris results from impairment in the balance between myocardial oxygen supply and demand. Myocardial oxygen demand is determined by the afterload and preload. The same factors that determine afterload by affecting the peripheral vascular resistance also affect the coronary arteries and therefore determine the myocardial blood supply. Elevated peripheral vascular resistance is also the main hemodynamic impairment in hypertension.

Antianginal drugs act mainly by 2 mechanisms: (1) reduction in myocardial oxygen demand; and (2) increase in myocardial blood supply. It is the delicate interplay between the pathophysiology in any individual patient and the relative effect of drugs on either mechanism that determines the suitability of a specific drug for an individual patient. Pretreatment systemic arterial pressure is a determinant of myocardial oxygen demand (afterload) and supply (coronary perfusion pressure). Obviously, it is a major factor affecting the therapeutic response to various antianginal drugs.

Except for nitrates, all antianginal drugs are also antihypertensive drugs. Calcium antagonists and β-adrenoreceptor blockers are even first-line antihypertensive drugs. Although their blood pressure–reducing effect is proportional to blood pressure before treatment, they can decrease blood pressure also in normotensive subjects. Nitrates lower myocardial oxygen demand by both afterload and preload reduction, and increase coronary supply by coronary dilation. Although they can decrease blood pressure they are not antihypertensive drugs.

CALCIUM ANTAGONISTS

Calcium antagonists are first-line antihypertensive drugs. They reduce blood pressure mainly by reducing the peripheral vascular resistance. This is also one of the mechanisms of their antianginal effect: They reduce myocardial oxygen demand by decreasing afterload. Their negative inotropic effect also contributes to a reduction of oxygen demands.[1–3] Another mechanism is an increase in myocardial oxygen supply due to coronary vasodilation.[4–6]

The main mechanism of the antianginal effect of calcium antagonists is reduction in afterload and myocardial oxygen demand and not an increase in coronary blood supply. This statement is based on the finding that despite an increase in exercise duration, calcium antagonists (nifedipine as well as diltiazem) do not increase the heart rate–systolic pressure product during maximal exercise.[7]

Blood pressure and myocardial contractility can be reduced only to a limited extent before the beneficial effect on myocardial oxygen demand is offset by a reduction in coronary perfusion and impairment of cardiac function. Therefore, additional mechanisms, including coronary vasodilation and preload reduction, are important.

Calcium antagonists are potent coronary dilators. In a recent study,[8] diltiazem was shown to increase exercise duration in association with a lower double product than did nicorandil, a nitrate ester. It is unlikely that nicorandil reduced coronary tone more than the potent coronary dilator diltiazem. Therefore, left ventricular preload reduction may be the mechanism responsible for higher values of double product obtained with the nitrate ester. In normotensive patients, it is preferable to use antianginal agents that increase exercise duration without excessive reduction in the double product and, mainly, in its blood pressure component.

Recently, the topic has been approached from the direction of combined treatment of hypertension and angina by 1 calcium antagonist in patients with both diseases. It has been shown, e.g., that nitrendipine is safe and effective in patients with both hypertension and angina pectoris by relieving angina, improving exercise tolerance and decreasing elevated blood pressure.[9] However, the opposite question regarding antianginal efficacy in normotensive and hypotensive patients has not been extensively addressed.

From The Cardiovascular Research Foundation, Geneva, Switzerland, and Barzilai Hospital, Ashkelon, Israel.

Address for reprints: Adam Schneeweiss, MD, Sauerberg 12, 6208 Bad Schwalbach 7, Federal Republic of Germany.

The potential problems associated with the use of potent systemic vasodilators such as calcium antagonists in patients with coronary artery disease are emphasized by (1) the phenomenon of "paradoxical angina"—an increase in the extent of angina in some patients with coronary artery disease treated with calcium antagonists.[10,11] In 1 study, nifedipine increased angina in 6 of 24 patients with chronic stable angina pectoris.[12] Although the real incidence of paradoxic angina is much lower, it is a serious adverse effect. The most likely explanation is excessive reduction in blood pressure and coronary perfusion pressure; and (2) the failure to show a consistent beneficial effect of calcium antagonists in secondary prevention,[13] mainly when given early in the course of acute myocardial infarction; this is probably related to excessive reduction in blood pressure in some patients, mainly those who were normotensive before drug administration. This hypothesis is supported by the tendency to excess mortality in infarct patients with systolic pressure ≤100 mm Hg found in the nifedipine secondary prevention trial.[14]

The significance of adverse effects associated with blood pressure reduction is emphasized when combined therapy with 2 calcium antagonists is compared to monotherapy with 1 such agent. In a study with nifedipine and diltiazem[15] patients receiving combination therapy had more adverse effects than those receiving either nifedipine or diltiazem monotherapy. Most adverse effects including dizziness, palpitation and aggravation of angina might have been related to reduction in blood pressure.

These findings indicate that calcium antagonists should not be the first antianginal drug in normotensive patients and certainly not in those who are hypotensive. Several ongoing clinical trials are comparing the antianginal effect of dihydrophyridine calcium antagonists in normotensive and hypertensive patients. A trial comparing the antianginal effect of nitrates and calcium antagonists in normotensive and hypertensive patients is indicated.

However, calcium antagonists can also reduce preload[16] and various calcium antagonists have different hemodynamic profiles. In the future certain calcium antagonists may be found more suitable than others for use in nonhypertensive patients.

BETA-ADRENORECEPTOR BLOCKERS

Beta-adrenoreceptor blockers are first-line antihypertensive agents. They also have a potent antianginal effect attributed to a decrease in myocardial oxygen demand due to slowing of heart rate, decreased contractility, reduced blood pressure and other mechanisms of minor importance.[17–20] Beta-adrenoreceptor blockers do not increase coronary blood supply. They may even cause coronary constriction, secondary to reduced oxygen demand.[21,22] They do not reduce the preload.

Beta-adrenoreceptor blockers are excellent antianginal drugs in hypertensive patients and in most normotensive patients. However, any agent that acts largely by decreasing blood pressure and depression of myocardial contractility must theoretically have limited efficacy in normotensive or hypotensive patients. This problem was not addressed in most studies evaluating β blockers as therapy for angina pectoris, because hypotensive patients were excluded and the results were not analyzed in relation to pretreatment blood pressure. It is possible that such an analysis would have revealed a greater effect in those with higher pretreatment pressure and a lesser, or even a negative effect, in normotensive and hypotensive patients.

This potential problem is seen also in the secondary prevention trials with β-adrenoreceptor blockers.[23–26] Overt and even borderline hypotensive patients have been excluded from these trials. Their inclusion might have theoretically caused some cases of death due to aggravation of ischemia, which could have offset the beneficial effect of β blockers in other postinfarction patients.

Studies comparing the antianginal effect of β blockers in hypertensive and normotensive patients are indicated. Until the results of such studies are available it is advisable to initiate treatment of angina pectoris in normotensive and hypertensive patients with other drugs.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Animal experiments have shown a reduction of ischemic insults by angiotensin-converting enzyme (ACE) inhibitors.[27–30] The mechanism of this effect could be afterload and preload reduction, an inhibitory effect on local catecholamine release, an effect on tissue renin-angiotensin system and even the negative inotropic effect of these agents. In patients who have had myocardial infarction, remodeling of the left ventricle can be modified with captopril.[31]

These findings have little relevance to treatment of angina pectoris. Any antianginal effect that ACE inhibitors might have is probably mainly related to afterload reduction. ACE inhibitors are first-line antihypertensive agents. The animal studies previously mentioned did not take into account the relation between pretreatment blood pressure and the effect of ACE inhibitors on ischemia. This question should be addressed directly by clinical trials in normotensive and hypertensive patients with angina pectoris and other ischemic presentations.

Until now these agents have been evaluated clinically mainly in patients with acute myocardial infarction and heart failure. Systemic hypotension was a significant problem in these studies. Mean arterial pressure decreased to <70 mm Hg in 3 of 7 patients in 1 study[32] and systolic arterial pressure decreased to <75 mm Hg in 21% of the patients in another.[33] In a third study mean arterial pressure decreased to <70 mm Hg in 50% of the patients.[34]

The effect of ACE inhibitors on myocardial ischemia in normotensive patients has been studied only recently. Gibbs et al[35] compared the effects of enalapril and placebo, each given for 2 weeks, in 12 such patients. Four of the patients prolonged their total exercise time ≥20%. Two patients, however, developed ischemia earlier during exercise and reduced their total exercise duration. Their exercise blood pressure did not differ from the patients

who had improvement. In conclusion, the effect of enalapril on myocardial ischemia is variable. Initiation of treatment with enalapril in normotensive patients with angina pectoris requires careful monitoring and could not, of course, be recommended clinically.

A more practical issue is the use of ACE inhibitors in normotensive patients with heart failure of ischemic etiology, with or without angina pectoris; this is the largest group of patients with heart failure. Gibbs et al[35] stated that "enalapril should be used with caution in treating heart failure caused by ischemic heart disease, since the beneficial effects of ACE inhibition on the heart failure may be offset if the myocardial ischemia is made worse."

Haude et al[36] reported that sublingual captopril improved angina and ST-segment depression, decreased diastolic pulmonary arterial pressure and increased cardiac output in 6 patients with unstable angina resistant to nitroglycerin. Captopril reduced mean arterial pressure in this group from 88 ± 12 to 74 ± 10 mm Hg. Because of the recent knowledge on the pathophysiology of unstable angina the practical implication of these findings is not definitive.

NITRATES

Nitrates are first-line antianginal but not antihypertensive drugs. Their mechanism of action includes coronary vasodilation,[37,38] preload and afterload reduction[39,40] and effects on the diastolic properties of the heart and on platelet function.[41] Nitrates do not rely so much on afterload reduction and reduction in blood pressure as do other antianginal agents. The effect on the coronary arteries is a "positive" vasodilation, i.e., dilation of the large coronary arteries including stenotic segments, thereby increasing the myocardial blood supply (in contrast to "negative" vasodilation of coronary resistance vessels, resulting in coronary steal). Nitrates also improve perfusion in myocardial zones dependent on collateral flow and in this effect they may be superior to other vasodilators, including calcium antagonists.[42] They can prevent the exercise-induced coronary vasoconstriction observed in patients with coronary artery disease.[43] Nitrates also make coronary flow more homogenous,[44] thus favoring ischemic zones over normal zones.

The main differences between nitrates and calcium antagonists are the greater preload reduction (relative to afterload reduction), the lack of a negative inotropic effect of nitrates and a somewhat different profile of the coronary effect.

Nitrates are not antihypertensive drugs. Although they decrease blood pressure acutely, this effect is largely attenuated during chronic use. The only instance in which nitrates are used, investigationally, for treatment of hypertension, is isolated systolic hypertension in the elderly.[45] In this condition the pathophysiology is different from that of the usual cases of essential hypertension, and is mainly related to stiffness of the conduit arteries. Even in this condition I was unable to find a marked blood pressure–reducing effect of nitrates (unpublished data).

All these findings indicate that nitrates are superior to other antianginal and anti-ischemic drugs for treatment of myocardial ischemia in normotensive patients. This recommendation is supported by the extremely low incidence of aggravation of ischemia during chronic oral nitrate therapy.[46]

COMBINED THERAPY

Combined therapy with β adrenoreceptors and calcium antagonists produces an additive antianginal effect only in patients with normal or mildly impaired left ventricular function who remain symptomatic despite optimal treatment with a single agent alone.[47] It is unlikely that normotensive agents, mainly with impaired left ventricular function, would benefit from combined therapy with potent blood pressure–reducing drugs. Packer[47] recommended that if patients with left ventricular dysfunction continue to experience pain during therapy with nitrates and β blockers, coronary artery bypass surgery rather than addition of a third drug should be considered. This is definitely the case for those who are also normotensive or hypotensive.

SUMMARY

All antianginal drugs except nitrates are also first-line antihypertensive drugs. Their antianginal efficacy has not been evaluated in relation to pretreatment blood pressure. They may aggravate ischemia due to excessive reduction in blood pressure. Until the results of direct comparative studies are available, it is advisable to start treatment of angina pectoris in normotensive and hypotensive patients with other drugs that do not primarily decrease blood pressure. Nitrates are a reasonable choice.

REFERENCES

1. Valter W. Myocardial oxygen consumption under the influence of nifedipine (adalat) in the anesthetized dog. In: Lochner W, Kronenberg G, eds. New Therapy of Ischemic Heart Disease. *Berlin: Springer Verlag, 1975:77–82.*

2. Stone PH, Antman EM, Muller JE, Braunwald E. Calcium channel blocking agents in the treatment of cardiovascular disorders. II. Hemodynamic effects and clinical applications. *Am J Cardiol 1979;44:811–814.*

3. Serruys PW. Influence of intracoronary nifedipine on left ventricular function, coronary vasomotility and myocardial oxygen consumption. *Br Heart J 1983;49: 427–434.*

4. Kellett MA. The effect of verapamil on coronary and systemic hemodynamics in patients with coronary heart disease. *Am J Cardiol 1982;49:896–900.*

5. Vatner SF, Hintze TH. Effects of a calcium channel antagonist on large and small coronary arteries in conscious dogs. *Circulation 1982;66(3):579–583.*

6. Schulz W, Wendt T, Klepzig H Jr, Kober G. Der Einfluss von intrakoronarem und intravenosem Nifedipine and die allgemeine und lokale Getassweite von epikardialen Koronararterien bei stabiler Angina pectoris—ein antianginoser Wirkaspekt? *Z Kardiol 1982;70:809–813.*

7. Wallace WA, Wellington KL, Murphy GW, Liang C-S. Comparison of antianginal efficacies and exercise hemodynamic effects of nifedipine and diltiazem in stable angina pectoris. *Am J Cardiol 1989;63:414–418.*

8. Nikoshita M, Hashimoto K, Ohbayashi Y, Inoue T, Taguchi H, Mitsunami K. Comparison of antianginal activity of nicorandil, propranolol and diltiazem with reference to the antianginal mechanism. *Am J Cardiol 1989;63:71J–74J.*

9. Schmoeckel M, Arendt RM, Hauck R, Schultheiss H-P. Acute and chronic effects of nitrendipine on hemodynamics and myocardial ischemia in patients with combined angina pectoris and hypertension. *J Cardiovasc Pharmacol 1988;12: suppl 4:S170–S174.*

10. Angelin PF. Hemodynamic and enzymatic effects of intravenous nifedipine administration in acute myocardial infarction. 5th International Adalat Symposium. In: Kaltenbach M, Neufeld HN, eds. New Therapy of Ischemic Heart Disease and Hypertension. *Amsterdam: Excerpta Medica, 1983:208–214.*

11. Fox KM. Treatment of chronic stable angina pectoris with nifedipine. 5th International Adalat Symposium. In: Kaltenbach M, Neufeld HN, eds. New Therapy of Ischemic Heart Disease and Hypertension. *Amsterdam: Excerpta Medica, 1983:197–208.*

12. Subramanian VB. Rationale for the choice of calcium antagonists in chronic stable angina. An objective double-blind placebo-controlled comparison of nifedi-

pine and verapamil. *Am J Cardiol 1982;50:1173–1178.*
13. The Israeli Sprint Study Group. Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT). A randomized intervention trial of nifedipine in patients with acute myocardial infarction. *Eur Heart J 1988;9:354–364.*
14. The Sprint Group: The Secondary Prevention Reinfarction Israeli Nifedipine Trial (Sprint II) (abstr). *Eur Heart J 1988;9:350.*
15. Frishman W, Charlap S, Kimmel B, Teicher M, Cinnamon J, Allen L, Strom J. Diltiazem, nifedipine, and their combination in patients with stable angina pectoris: effects on angina, exercise tolerance, and the ambulatory electrocardiographic ST segment. *Circulation 1988;77(4):774–786.*
16. Yokota M, Koide M, Miyahara T, Kamihara S, Tsunekawa A, Noda S, Sotobata I. Effects of a new second generation calcium channel blocker, nilvadipine (FR34235), on exercise-induced hemodynamic changes in stable angina pectoris. *J Am Coll Cardiol 1987;10:830–836.*
17. Smith HJ, Goldstein RA, Griffith JM, Epstein SE. Regional contractility: selective depression of ischemic myocardium by verapamil. *Circulation 1976; 54:629–635.*
18. Friedman MJ, Temkin LP, Goldman S, Ovitt TW. Effects of propranolol on resting and post extra systolic potentiated left ventricular function in patients with coronary artery disease. *Am Heart J 1983;106:81–84.*
19. Port S, Gobb FR, Jones RH. Effects of propranolol on left ventricular function in normal men. *Circulation 1980;61(2):358–365.*
20. Milne JR, Camm AJ, Ward DE, Spurrell RAJ. Effect of intravenous propranolol on QT interval: a new method of assessment. *Br Heart J 1980;43:1–7.*
21. Davids WG, Macdonald DC, Mason DFJ. Effects of pronetholol and propranolol on the coronary circulation of the dog. *Br J Pharmacol 1969;37:338–342.*
22. Kern MJ. Potentiation of coronary vasoconstriction by beta-adrenergic blockade in patients with coronary artery disease. *Circulation 1983;67(6):1178–1184.*
23. Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med 1981;304:801–807.*
24. Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction: I. Mortality results. *JAMA 1982;247:1707–1714.*
25. Rehnqvist N, Olsson G. Influence on ventricular arrhythmias by chronic post-infarction treatment with metoprolol (abstr). *Circulation 1983;68:suppl III:III-369.*
26. The MIAMI Trial Research Group. Metoprolol in acute myocardial infarction (MIAMI). A randomized placebo-controlled international trial. *Eur Heart J 1985;6:199–226.*
27. Ertl G, Kloner RA, Alexander RW, Braunwald E. Limitation of experimental infarct size by an angiotensin-converting enzyme inhibitor. *Circulation 1982;65:40–48.*
28. Van Gilst WH, De Graeff PA, Wesseling H, De Langen CDJ. Reduction of reperfusion arrhythmias in the ischemic isolated rat heart by angiotensin converting enzyme inhibitors: a comparison of captopril, enalapril, and HOE 498. *J Cardiovasc Pharmacol 1986;8:722–728.*
29. Van Gilst WH, De Graeff PA, Kingma JH, Wesseling H, De Langen CDJ. Captopril reduces purine loss and reperfusion arrhythmias in the rat heart after coronary artery occlusion. *Eur J Pharmacol 1984;100:113–117.*
30. Linz W, Schölkens BA, Han Y-F. Beneficial effects of the converting enzyme inhibitor, ramipril, in ischemic rat hearts. *J Cardiovasc Pharmacol 1986;8:suppl 10:91–99.*
31. Pfeffer JM, Pfeffer MA, Braunwald E. Influence of chronic captopril therapy on the infarcted left ventricle of the rat. *Circ Res 1985;57:84–95.*
32. McAlpine HM, Morton JJ, Leckie B, Dargie HJ. Use of oral ACE inhibitors post infarct. *J Cardiovasc Pharmacol 1987;9:suppl 2:25–30.*
33. Wenting GJ, Man in't Veld AJ, Woittiez AJ, Derkx FHM, Schalekamp MADH. Captopril in the treatment of severe acute and chronic heart failure. *Progr Pharmacol 1984;5:107–122.*
34. Brivet F, Deltraissay J, Gindicelli J, Richer C, Legrand A, Dormont J. Immediate effects of captopril in acute left ventricular failure secondary to myocardial infarction. *Eur J Clin Invest 1981;11:369–373.*
35. Gibbs JSR, Crean PA, Mockus L, Sutton GC, Fox KM. The variable effects of angiotensin converting enzyme inhibition on myocardial ischaemia in chronic stable angina (abstr). *Eur Heart J 1989;10:suppl 3:5.*
36. Haude M, Erbel R, Tschollar W, Meyer J. Sublingual captopril in patients with unstable angina (abstr). *Eur Heart J 1989;10:suppl 3:5.*
37. Brown BG, Bolson E, Petersen RB, Pierce DC, Dodge HT. The mechanisms of nitroglycerin action: stenosis vasodilation as a major component of the drug response. *Circulation 1981;64:1089–1097.*
38. Simon R, Koch M, Reil G. Effect of intracoronary nitroglycerin on coronary vascular volume in man assessed by a double indicator method (abstr). *Eur Heart J 1987;8:suppl 1:22.*
39. Goldstein RE, Bennett ED, Leech GL. Effect of glyceryl trinitrate on echocardiographic left ventricular dimensions during exercise in the upright position. *Br Heart J 1979;42:245–254.*
40. Fuchs RM, Brinker JA, Guzman PA, Kross DE, Yin FCP. Regional coronary blood flow during relief of pacing-induced angina by nitroglycerin. *Am J Cardiol 1983;51:19–23.*
41. De Caterina R, Gianessi D, Crea F, Chierchia S, Bernini W, Gazzetti P, L'Abbate A. Antiplatelet effects of isosorbide dinitrate in man. *Z Kardiol 1983;72:suppl 3:46–51.*
42. Fujita M, McKown DP, McKown MD, Franklin D. Comparative effects of nitroglycerin and diltiazem on regressed, newly developed coronary collaterals in conscious dogs (abstr). *J Am Coll Cardiol 1986;7:suppl:53A.*
43. Krayenbühl HP, Hess OM, Gage JE, Grimm J. Nitroglycerin prevents coronary artery stenosis narrowing during dynamic exercise. *Eur Heart J 1987;8:suppl 1:23.*
44. Engle HJ, Wolf R, Pretschner P, Hundeshagen H, Lichtlen PR. Effect of nitrates on myocardial blood flow during angina: comparison of results obtained by inert gas clearance and 201 thallium imaging. In: Lichtlen PR, Engel H, Schrey A, Swan HJC, eds. Nitrates III. *Berlin: Springer-Verlag, 1981:184–191.*
45. Duchier J, Iannascoli M, Safar ME. Antihypertensive effect of sustained-release isosorbide dinitrate in elderly patients with systolic hypertension. X World Congress of Cardiology, Washington DC, September 14–19, 1986(2796).
46. Schneeweiss A, Weiss M. Advances in Nitrate Therapy. *Berlin, Heidelberg: Springer-Verlag, 1988.*
47. Packer M. Combined beta-adrenergic and calcium-entry blockade in angina pectoris. *N Engl J Med 1989;320(11):709–718.*

Evaluation of the Efficacy and Duration of Action of Isosorbide Mononitrate in Angina Pectoris

Mark A. de Belder, MD, Adam Schneeweiss, MD, and A. John Camm, MD

The magnitude and duration of the antianginal and anti-ischemic effects of isosorbide mononitrate (IS-5-MN), 20 mg, were determined in 10 patients with chronic stable angina pectoris. An exercise test (treadmill, Bruce protocol) was performed before and at 1, 6, 8 and 10 hours after oral administration of the drug. The patients were randomly assigned to receive IS-5-MN or placebo, and after 1 week of therapy were crossed over to the other formulations. The drug increased the exercise duration from 321 to 455 seconds at 1 hour ($p < 0.001$). Time to moderate angina increased from 237 to 324 seconds ($p < 0.05$) and time to ST depression ≥1 mm increased from 150 to 307 seconds ($p < 0.01$) at 1 hour. Placebo had no effect on any of the exercise parameters. Although partially attenuated at 6 hours, the effect of IS-5-MN remained statistically significant even at 8 hours, but not at 10 hours. It is concluded that the duration of action of a single tablet of IS-5-MN, given orally, is 8 hours.

(Am J Cardiol 1990;65:6J–8J)

The organic nitrates are often the first choice of physicians for the management of patients with angina pectoris. Nitroglycerin (NTG) is usually administered sublingually for episodes of angina pectoris but its short duration of action generally makes it unsuitable for prophylactic use. Isosorbide dinitrate (ISDN) is also an effective antianginal agent but has low bioavailability after oral administration and there are marked interindividual variations in plasma concentrations after oral administration.[1–5] Isosorbide-5-mononitrate (IS-5-MN), an active metabolite of ISDN, does not undergo first-pass hepatic metabolism and thus is completely bioavailable.[6] IS-5-MN has linear kinetics for doses of 10 to 80 mg.[7,8] The interindividual variations in plasma concentrations after IS-5-MN administration are less than 30% and the plasma half-life is between 4 and 6 hours,[4,9] approximately 8 times that of ISDN. Initial studies have shown that single doses of IS-5-MN exert antianginal and anti-ischemic effects.[10–13]

This report describes a study designed to assess the magnitude and duration of the effect of IS-5-MN (20 mg) on exercise capacity and electrocardiographic evidence of myocardial ischemia in patients with chronic stable angina pectoris.

METHODS

Patients: Ten men (aged 36 to 68 years) with chronic stable angina were studied. All patients had (1) a history of typical, stable exertional angina pectoris for ≥2 months before the study; (2) development of typical chest pain during treadmill exercise testing and the presence of ≥1 mm of ST-segment depression (flat or downsloping ST segments for ≥80 ms after the J point); (3) documentation of coronary artery disease or myocardial ischemia, or both, by 1 of the following criteria—documented myocardial infarction, coronary arteriographic documentation of significant coronary artery disease (≥75% narrowing of at least 1 major artery), positive findings on thallium perfusion stress testing; (4) moderate angina between 3 and 9 minutes on the Bruce protocol; (5) reproducibility of exercise results, defined as 2 consecutive exercise tests with an end point of moderate angina within 15%; and (6) demonstration of nitrate responsiveness as documented by prolongation of treadmill exercise time by ≥20% when exercise testing is performed 5 minutes after sublingual administration of 0.4 mg of NTG.

The following exclusion criteria were used: (1) myocardial infarction or cardiac surgery within 3 months, (2) congestive heart failure, (3) digitalis administration, (4) atrial or ventricular dysrhythmias requiring antiarrhythmic therapy, (5) hypertension (blood pressure >170/100 mm Hg) or patients requiring antihypertensive therapy

From the Department of Cardiological Sciences, St. George's Hospital Medical School, London, United Kingdom and the Cardiovascular Research Foundation, Geneva, Switzerland.

Address for reprints: A. John Camm, MD, Department of Cardiological Sciences, St. George's Hospital Medical School, Cranmer Terrace, Tooting, London SW17 0RE, United Kingdom.

TABLE I Changes in Duration of Exercise Test*

Variable/Statistics	PLAC/0	ISMN/0	PLAC/1H	ISMN/1H	PLAC/6H	ISMN/6H	PLAC/8H	ISMN/8H	PLAC/10H	ISMN/10H
Exercise duration (sec)										
Mean	324	321	330	455	291	340	311	345	299	309
SD	144	125	137	136	113	132	122	119	125	124
No. of Pts.	10	10	10	10	10	10	10	10	10	10
DIFF. ABS.		−3		125§		49‡		34†		10
DIFF. IN %		−0.9		37.9		16.8		10.9		3.3

* Exercise duration before and 1 (0), 6 (6H), 8 (8H) and 10 (10H) hours after administration of placebo (PLAC) and isosorbide mononitrate (ISMN).
† $p < 0.05$; ‡ $p < 0.01$; § $p < 0.001$.
DIFF. ABS. = absolute difference (sec); DIFF. IN % = percentage difference; SD = standard deviation.

other than diuretics to attain this blood pressure level, (6) significant valvular disease, and (7) anemia (hemoglobin <11 g).

Study design: Patients were fully informed about the investigation and signed a consent form before being enrolled in this investigation. The trial was approved by the Institutional Ethics Committee. All long-acting antianginal drugs were discontinued 1 week before the study.

Exercise test: Patients underwent treadmill testing using the Bruce protocol. They came to the laboratory in the fasting state without taking their morning medications and not taking NTG for at least 2 hours. During exercise testing the following observations were made: (1) time to the onset of angina and to the development of moderate angina at which point exercise was discontinued; and (2) blood pressure recording by sphygmomanometry at the end of each exercise stage, at the time of the onset of angina and at the point of cessation of exercise. Exercise was terminated at the development of moderate angina.

Study protocol: When the reproducibility of exercise testing had been demonstrated and the patient had been shown to be a nitrate responder, the definitive investigation was begun. The patient came to the laboratory at 8 A.M. in the fasting state and having taken no medications and no NTG for ≥2 hours. A control exercise test was performed as described. Thirty minutes later, in a double-blind, crossover, placebo-controlled fashion, either one 20-mg tablet of IS-5-MN or placebo was administered with 60 ml of water. Treadmill exercise testing as previously described was performed at 1, 6, 8 and 10 hours after dosing.

Statistical analysis: The data were analyzed using paired *t* test and analysis of variance. The efficacy of IS-5-MN over the 10-hour observation period compared with placebo was evaluated.

RESULTS

All patients completed the trial. Placebo had no effect on any of the exercise parameters. IS-5-MN increased exercise duration (Table I) from 321 to 455 seconds at 1 hour after the dose ($p < 0.001$). This effect was partially attenuated at 6 hours (340 seconds) but remained significant ($p < 0.01$). The prolongation of exercise duration was still significant even at 8 hours (345 seconds, $p < 0.05$) but not at 10 hours. Time to moderate angina (Table II) increased from 237 ± 86 to 324 ± 153 seconds ($p < 0.05$) at 1 hour. This change was attenuated at 6 hours to 283 ± 107 seconds, but remained significant at this time and at 8 hours, but not at 10 hours. Time to ST-segment depression of ≥1 mm increased from 150 ± 64 to 307 ± 109 seconds ($p < 0.01$) at 1 hour but was attenuated at 6 hours. No serious adverse effects were observed during the trial.

TABLE II Changes in Time to Angina Pectoris (AP) and to ST Depression of ≥0.1 mm

Variable/Statistics	PLAC/0	ISMN/0	PLAC/1H	ISMN/1H	PLAC/6H	ISMN/6H	PLAC/8H	ISMN/8H	PLAC/10H	ISMN/10H
Time to AP (sec)										
Mean	172	181	196	334	175	238	181	239	187	202
SD	54	80	74	119	71	87	55	70	73	82
No. of Pts.	9	9	9	9	9	9	9	9	9	9
DIFF. ABS.		9		138‡		63‡		58‡		15
DIFF. IN %		5.2		70.4		36.0		32.0		8.0
Time to moderate AP (sec)										
Mean	222	237	229	324	210	283	244	283	231	259
SD	71	86	70	153	76	107	85	97	86	103
No. of Pts.	9	9	9	9	9	9	9	9	9	9
DIFF. ABS.		15		95†		73‡		39†		28
DIFF. IN %		6.8		41.5		34.8		16.0		12.1
Time to ST depress. (sec)										
Mean	165	150	165	307	135	165	150	173	150	150
SD	62	64	77	109	53	83	85	59	56	64
No. of Pts.	8	8	8	8	8	8	8	8	8	8
DIFF. ABS.		−15		142‡		30		23		0
DIFF. IN %		−9.1		96.1		22.2		15.3		0.0

* Time to angina pectoris and to ST depression of 1 mm before (0) and 1 (1H), 6 (6H), 8 (8H) and 10 (10H) hours after placebo (PLAC) and isosorbide mononitrate (IS-5-MN).
† $p < 0.05$; ‡ $p < 0.01$.
Depress. = depression; other abbreviations as in Table I.

DISCUSSION

Several parameters affect the optimal dose in nitrate therapy. Among these are the magnitude of the effect, the short duration of the effect (which is partially dose related) and the attempt to prevent tolerance.[14] The optimal dose should be large enough to exert maximal or near maximal effect, and small enough to prevent tolerance (which is directly related to the dose[13]). The duration of action of each dose should be studied specifically, because in most efficacy studies the magnitude of effect was measured at 1 or 2 hours after administration but its duration was not determined.

Previous studies revealed that the optimal oral dose of the conventional formulation of IS-5-MN is 20 mg.[15] Our study confirms antianginal and anti-ischemic efficacy of this dose. We have also shown that peak effect occurs at 1 hour after oral administration. Our design does not exclude, however, the possibility that a somewhat greater effect would have been observed at 2 hours. The initial effect of IS-5-MN during exercise parameters was partially attenuated at 6 hours, but remained statistically significant at this time and even at 8 hours. At 10 hours the effect was almost completely attenuated.

Our results indicate that the duration of action of oral IS-5-MN, 20 mg, in patients with chronic stable angina is 8 hours. A regimen of 20 mg twice daily may be suitable for long-term treatment of patients with exertional angina during the day.

REFERENCES

1. Thadani U, Fung H, Darke AC, Parker JO. Oral isosorbide dinitrate in angina pectoris: comparison of duration of action and dose-response relation during acute and sustained therapy. *Am J Cardiol 1980;49:411–419.*

2. Assinder DF, Chasseaud LF, Taylor T. Plasma isosorbide dinitrate concentrations in human subjects after administration of standard and sustained release formulations. *J Pharm Sci 1977;66:775–778.*

3. Fung H, McNiff EF, Ruggirello D, Darke A, Thadani U, Parker JO. Kinetics of isosorbide dinitrate and relationship to pharmacological effects. *Br J Clin Pharmacol 1981;11:579–590.*

4. Chasseaud LF. Newer aspects of the pharmacokinetics of organic nitrates. *Z Kardiol 1983;72:suppl 3:20–23.*

5. Taylor T, Chasseaud LF, Doyle E, Bonn R, Darragh A, Lambe RF. Isosorbide dinitrate pharmacokinetics. *Arzneimittelforschung 1982;32:1329–1333.*

6. Abshagen U, Btzien G, Endele R, Kaufmann B. Pharmacokinetics of intravenous and oral isosorbide-5-mononitrate. *Eur J Clin Pharmacol 1981;20:269–275.*

7. Kenedi P. Intraindividuelle Dosiswirkungsbeziehung von elantan long. In: Borchard U, Rafflenbeul W, Schrey A, eds. Mononitrat. *München: Universitätsdruckerei und Verlag Dr C Wolf und Sohn, 1985:108–115.*

8. Abshagen U. Pharmacokinetics of ISDN, sustained-release ISDN and IS-5-MN. In: Cohn JN, Rittinghausen R, eds. Mononitrates. *Berlin: Springer-Verlag, 1985:53–66.*

9. Straehl P, Galeazzi RL, Soliva M. Isosorbide-5-mononitrate and isosorbide-2-mononitrate kinetics after intravenous and oral dosing. *Clin Pharmacol Ther 1984;36:485–492.*

10. Rennhak U, Riebesel T, Biamino G. A double-blind cross-over study on the effectiveness and possible development of tolerance during long-term therapy with isosorbide-5-mononitrate or isosorbide dinitrate slow-release in coronary artery disease. In: Cohn JN, Rittinghausen R, eds. Mononitrates. *Berlin: Springer-Verlag 1985:147–153.*

11. Menzel M. Ein-Jahresstudie mit Elantan Bei Patienten mit koronarer Herzerkrankung—Wirksamkeit und Verträglichkeit im Rahmen einer Langzeitbehandlung. In: Hochrein H, Tauchert M, Schrey A, Weiss M, eds. Mononitrat. *München: Universitätsdruckerei und Verlag Dr C Wolf und Sohn, 1984:98–111.*

12. Heepe W. Langzeittherapie der Patienten mit koronarer Herkrankheit mit IS-5-MN retard. In: Hochrein H, Tauchert M, Schrey A, Weiss M, eds. Mononitrat. *München: Universitätsdruckerei und Verlag Dr C Wolf und Sohn, 1984: 172–229.*

13. Tauchert M, Jansen W, Osterspey A, Fuchs M, Hombach V, Hilger HH. Dose dependence of tolerance during treatment with mononitrate. *Z Kardiol 1983;72:suppl 3:218–228.*

14. Schneeweiss A, Weiss M. Advances in Nitrate Therapy. *Berlin, Heidelberg, New York, London, Paris, Tokyo: Springer-Verlag 1988:99–110.*

15. Akhras F, Jackson G. Isosorbide-5-mononitrate as monotherapy in patients with chronic stable angina (abstr). *J Am Coll Cardiol 1986;7:230A.*

Long-Term Efficacy of Nitroglycerin Patch in Stable Angina Pectoris

Raffaele Greco, MD, Mario Schiattarella, MD, Simona Wolff, MD, Doriana D'Alterio, MD, and Pio Tartaglia, MD

Subchronic and chronic efficacy of a 10 mg of nitroglycerin (NTG) patch was studied in 30 patients with stable angina pectoris. The trial consisted of 2 periods of study: 1 period of 2 months with a double-blind, crossover, placebo-controlled design and a second period of open treatment with verum patch. Two 7-day washout periods were performed at entry and at the end of the study. Efficacy was evaluated by clinical assessment of anginal attacks and NTG consumption and by means of multistage treadmill exercise testing. Exercise tests were performed at time 0 (24 hours from application of last patch), at 4 and 12 hours after dosing at the end of first 7-day washout, at the end of first month of treatment, at the end of the second month of treatment after crossover, at the end of 3 months of treatment with active patch and at the end of the second 7-day washout period. Statistics were obtained by multivariate analysis of difference. In 27 patients whose records were available for final analysis the daily attacks of angina and NTG consumption decreased significantly during both the subchronic and chronic phases of the trial compared with placebo ($p < 0.001$). Subchronic study showed significant improvement of maximal exercise duration, time to onset of angina, time to ST-segment depression of 1.0 mm, time to regression of angina and time to regression of ST depression, compared with placebo. The efficacy was maintained during 3 months of chronic therapy but a certain degree of attenuation of effects was observed for some parameters: Duration of exercise and time of onset of angina was slightly but not significantly reduced during the chronic compared with the subchronic phase; time to regression of angina and ST-segment depression significantly increased at the end of the chronic trial compared with results in the subchronic phase. Thus, some degree of attenuation of effects occurred but not to a degree that would abolish all beneficial effects of treatment with NTG patch. The association with other drugs, for which the dosing regimen was maintained constantly throughout the entire study, may be one of the possible explanations for lack of tolerance in our study.

(Am J Cardiol 1990;65:9J–15J)

In recent years, modern pharmacology has made several attempts to develop new drug delivery systems that might be more acceptable to patients, thus improving compliance. These attempts have been successful with a number of drugs such as pilocarpine, progesterone, scopolamine, estradiol, clonidine and nitroglycerin (NTG). Transdermal NTG delivery systems, relying upon polymeric membranes, have found large acceptance among both patients and doctors, but at the same time, a brisk debate has arisen on its efficacy, the duration of its effects and tolerance development.

Tolerance, defined as increased dose requirement in order to obtain a certain therapeutic effect or decreased effect with the same dose, has been described for all organic nitrates regardless of their galenic preparation. Clinical studies on NTG patches, based mainly on the impact on the number of daily attacks of angina and NTG tablet consumption, failed to show a considerable loss of therapeutic effect for periods of treatment ranging from 1 month to 1 year.[1–3]

On the other hand, well-designed studies based on objective evidence of an anti-ischemic effect by exercise test results as well as clinical response have shown rapid, and sometimes complete, attenuation of vascular and therapeutic effects of nitrates after a period of continuous administration, whichever the therapeutic form.[4–11] Therefore, particular schedules of administration that might circumvent this problem have been suggested.[12]

Other well-designed, randomized, placebo-controlled studies have supplied evidence for persistence of efficacy in patients with angina pectoris, heart failure and silent ischemia.[13–21]

In this study we addressed this subject using Deponit-10® patch, which in a previous investigation by our group[22] was effective on a short-term basis in patients with stable angina pectoris. The complex protocol of this trial consists of a first part, a double-blind, placebo-controlled study lasting 2 months, and a second part, with an open design lasting 3 months in order to avoid the long-term use of placebo.

METHODS

The study population consisted of 30 men, aged 40 to 63 years (mean 52.0) with chronic, stable, effort, NTG-

From the Division of Cardiology, Ospedale Monaldi, Naples, Italy.
Address for reprints: Raffaele Greco, MD, Viale Winspeare 19 Vomero, 80127 Naples, Italy.

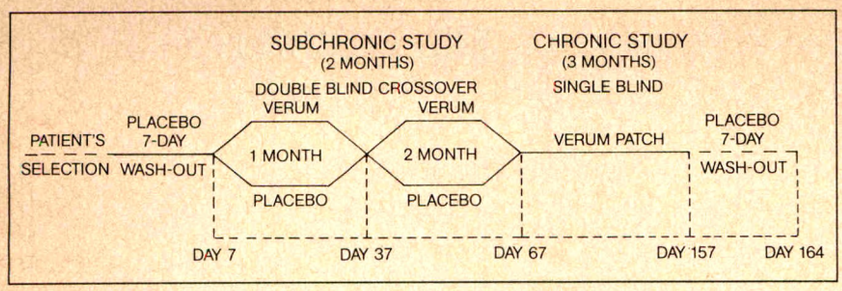


FIGURE 1. Trial design.

responsive angina pectoris for ≤6 months. Patients entered the study after giving informed consent and after having been tested for responsiveness to transdermal therapy (≥10% improvement in exercise duration with NTG patch at 4 and 12 hours). All patients were familiar with the treadmill technique and were followed on an outpatient basis. Coronary artery disease had been documented by a previous myocardial infarction (19 = 63.3%), angina pectoris (100%), coronary angiography (24 = 80%) and exercise testing (100%). Therapy with β blockers and calcium antagonists, antiplatelets and anticoagulants was kept unchanged during the trial in 20 patients (66.6%), whereas nitrates were restricted to NTG only as needed. If angina changed pattern at any time of the trial, patients were prematurely withdrawn from the study and assigned to a different therapy.

Exclusion criteria were angina at rest or mixed angina or infarction within the previous 3 months, need for antihypertensive therapy or organic nitrates other than sublingual NTG, and treatment with digitalis, diuretics or antiarrhythmic drugs, cardiomyopathy, valvular or lung disease, or any other disease of major significance. Other exclusion criteria were ST-segment depression at rest or other abnormal results on the electrocardiogram (ECG) which would have interfered with proper interpretation of the ECG during exercise: bundle branch block, left ventricular hypertrophy, Wolff-Parkinson-White syndrome, atrioventricular conduction defects, Q waves or tiny R waves on all precordial leads, and frequent or complex arrhythmias either on the ECG at rest or during the qualifying exercise test.

All patients were instructed to keep a diary of daily attacks of angina, NTG consumption and duration of each attack.

Study design: The trial covered a period of 164 days (Fig. 1) and consisted of a first 7-day washout placebo period during which patients discontinued to take nitrates but continued to take β blockers, calcium antagonists or antiplatelet drugs. At the end of this period patients underwent 3 treadmill tests on the seventh day: one at time 0 (24 hours from last application of patch), one at 4 and another at 12 hours from application of the last placebo patch. Afterward, a first part of the 60 days began with a placebo, controlled, double-blind crossover design during which patients were randomized to either a 1-month period with placebo or to a 1-month period with active patch. At the end of this first month of treatment patients underwent 3 treadmill tests as previously mentioned and crossed over to the other patch in the trial. At the end of this second-month period patients again underwent 3 exercise tests as previously indicated.

After completing this first part of the trial, a second part with open treatment with active patch started and lasted 90 days, at the end of which 3 more exercise tests were performed with the procedures already mentioned. Finally, a second period of washout with placebo took place for 7 days, and on the last day exercise testing was repeated at 0 time and at 4 and 12 hours from last patch application.

The patients were instructed to apply a new patch on the thorax immediately at the scheduled time after removing a previous patch. Tests were performed either in the morning (0 time and 4-hour test) or in the evening (12-hour test) in the postabsorption state. During 3 months of chronic therapy the patients were examined on a monthly basis and were encouraged to contact the medical staff frequently in order to obtain maximal compliance and adherence to the complex experimental protocol.

Experimental procedures: Exercise tests were performed on the treadmill according to the Bruce multistage protocol with the patient having taken no food or

TABLE I Changes in the Number of Attacks of Angina, Duration and Nitroglycerin (NTG) Consumption

Variables	PI	DSc	Δ%	DLt (1 mo)	Δ%	DLt (2 mo)	Δ%	DLt (3 mo)	Δ%
Attacks of Ang. No./mo	12.7 ± 3.5	8.1 ± 2.8	−36.2	8.0 ± 3.2	−37.0	7.2 ± 3.3	−43.3	7.1 ± 3.5	−44.1
Duration of Ang. min/mo	42.3 ± 12.2	26.9 ± 11.7	−36.4	25.8 ± 12.4	−39.9	23.9 ± 12.2	−43.5	25.3 ± 14.6	−40.2
NTG tablets No./mo	11.7 ± 4.3	7.2 ± 3.4	−38.5	6.4 ± 3.5	−45.3	6.3 ± 3.9	−46.2	7.0 ± 4.3	−40.2

All differences in this table are significant with a p value ≤0.001 compared with placebo.
All values are expressed as mean ± standard deviation.
Ang. = angina; DLt = long-term trial with Deponit at 1, 2 and 3 months; DSs = subchronic trial with Deponit-10; PI = placebo; Δ% = change percent.

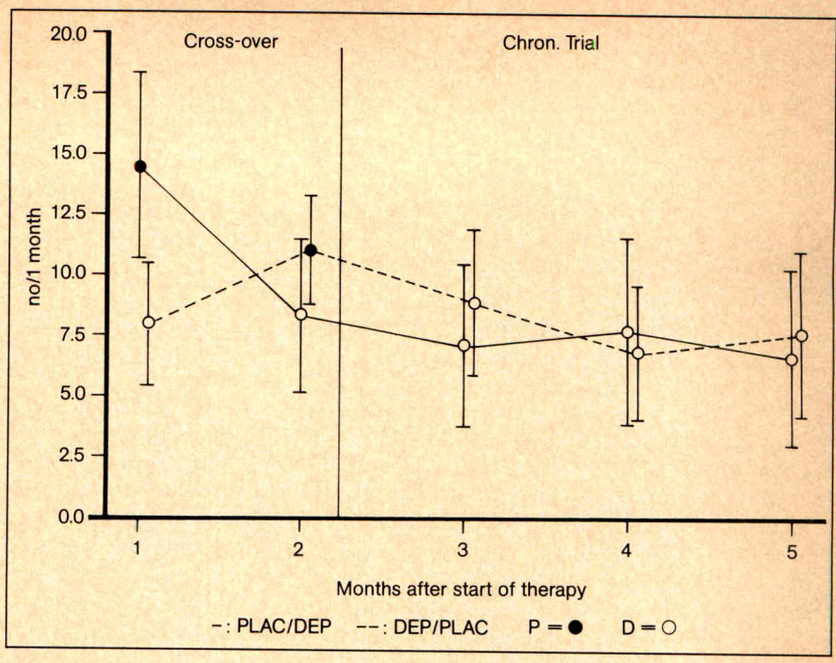


FIGURE 2. Daily attacks of angina pectoris (AP): number of attacks per month during the crossover subchronic trial and during the 3-month chronic (Chron.) trial. Placebo (PLAC) vs Deponit (DEP). D = Deponit; P = placebo.

beverages for ≥3 hours and taking customary medications. A 9-lead ECG (all limb leads and 3 precordial leads (V_1, V_4 V_6) was monitored continuously (3 leads at a time) and recordings were obtained at the end of each stage, at the end of exercise, during ischemic threshold (ST depression, 1 mm), at onset of angina and each minute for 10 seconds during recovery; blood pressure was measured at 1-minute intervals by cuff sphygmomanometer and by the same operator. Recovery was monitored with the patient in the standing position up to 10 minutes or until regression of any signs or symptoms. The exercise was gradually terminated within the first minute of recovery. Patients were instructed to indicate immediately the time of onset of angina or any other symptom as well as the time of its termination.

End points were typical angina of moderate severity and increasing with exercise, marked dyspnea, exhaustion, life-threatening arrhythmias, symptoms of cerebral hypoxia or gait disturbance, failure of systolic pressure to increase for 2 consecutive stages, decrease in systolic pressure while exercising, conduction defects, horizontal or downsloping ST-segment depression >2 mm and lasting >0.08 second after the J point, blood pressure >220/100 mm Hg, and upsloping of ST segment in any lead

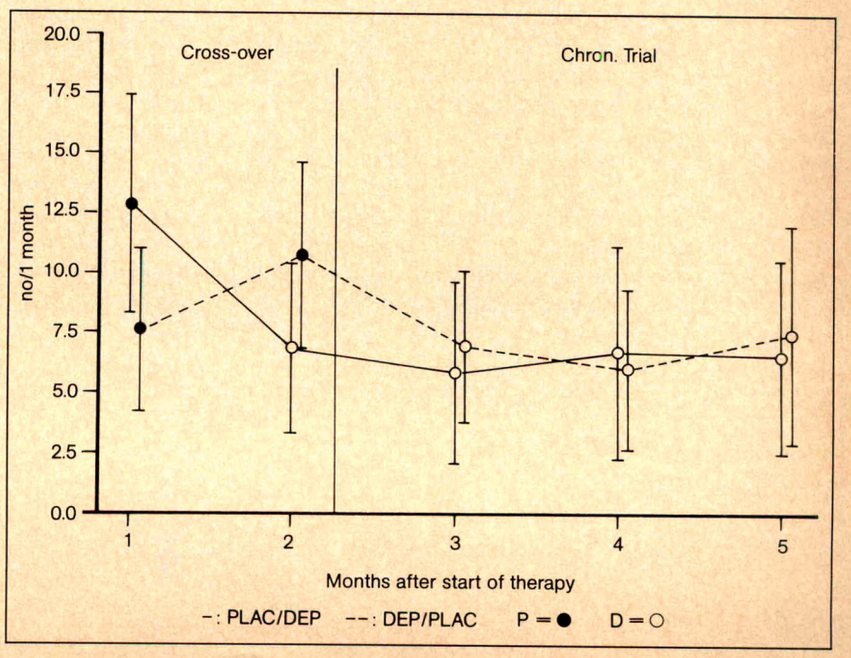


FIGURE 3. Additional consumption of nitroglycerin. Abbreviations as in Figure 2.

TABLE II Exercise Variations Under Placebo or Deponit-10: Subchronic Trial

Exercise Variables	Time 0			4 Hours			12 Hours		
	PL	D	Δ%	PL	D	Δ%	PL	D	Δ%
Duration	324 ± 80	383 ± 108	18.2‡	339 ± 107	448 ± 127	32.2†	302 ± 78	420 ± 121	39.1‡
Time to AP	245 ± 70	284 ± 92	15.9†	251 ± 57	343 ± 105	36.7*	237 ± 65	319 ± 98	34.6*
Time to APR	94 ± 41	61 ± 16	−35.1*	92 ± 43	68 ± 20	−24†	92 ± 33	67 ± 18	−27.2†
Time to IT	256 ± 80	291 ± 99	13.7*	247 ± 75	340 ± 114	37.7†	236 ± 82	333 ± 111	41.1†
Time to STR	355 ± 137	295 ± 124	−16.9*	371 ± 139	281 ± 90	−24.3†	406 ± 221	286 ± 114	−29.6‡

* $p \leq 0.05$; † $p \leq 0.01$; ‡ $p \leq 0.001$.
All times are expressed in seconds.
AP = angina pectoris; APR = regression of angina; D = Deponit-10; IT = ischemic threshold (ST displacement = 1 mm) downward; Pl = placebo; STR = regression of ST abnormality.

without Q waves related to previous myocardial infarction. Heart rate was measured on the ECG. Parameters used for evaluation were: exercise duration, time to onset of angina, time to ST depression (ischemic threshold) of 1 mm, time to disappearance of angina, time to regression of ST depression to baseline, heart rate, systolic blood pressure and double product. At each session, heart rate and blood pressure were recorded in the supine and upright positions. All exercise results were evaluated by attending cardiologists blindly and separately.

The main criteria for evaluating clinical efficacy were the change in the number of attacks of angina per week, the number of NTG tablets consumed and the duration of the attacks.

Statistical analysis: Analysis of quantitative differences between the placebo period and subchronic trial, and between subchronic and chronic trials was performed by multivariate analysis, each subject serving as his own control. The differences were calculated toward placebo value as a reference point and the significance of statistical analysis was determined at $p < 0.05$.

RESULTS

The trial was prematurely interrupted in 3 patients because of worsening angina pectoris, and other therapy was instituted. One patient was at his second week of treatment with the active patch, having completed the first arm of the randomized part with placebo. Another patient was in the third week of placebo after completing the month with Deponit and the third patient was in the first week of placebo after the month with active patch.

A fourth patient failed to attend all exercise sessions, but his diary was available for clinical evaluation of daily angina and NTG consumption. Thus, 26 patients completed the full trial and were analyzed for clinical and exercise data, and 27 patients were analyzed for clinical results.

No accidents or deaths occurred during the trial and during the exercise sessions. One of the 3 patients who interrupted the trial underwent coronary artery bypass surgery. Headache lasting 1 to 4 hours was observed in 8 patients during the first few days of active treatment and in 4 patients a skin erythema requiring no treatment developed. Heart rate and systolic blood pressure at rest decreased 3 to 5% ($p < 0.05$), changing from supine to standing position during the active treatment. Differences after the chronic trial were not statistically significant.

Antianginal effect: In 27 patients who completed the clinical trial (90%) the daily attacks of angina decreased significantly ($p < 0.001$) during both the subchronic (36.2%) and the chronic (37 to 44%) trial (Table I, Fig. 2).

Consumption of NTG also decreased significantly ($p < 0.001$) during both periods of study: 38.5% during the first part and 40 to 46% during the 3 months of the second part (Fig. 3). Duration of attacks was reduced during all periods of treatment compared with placebo (Table I).

Exercise testing: Table II shows changes of exercise variables during the subchronic, double-blind, crossover part of the trial. Duration increased at any time from application of active patch: 18.2% at 0 time, 32.2% at 4 hours and 39.1% at 12 hours. A similar finding was observed for other parameters of exercise performance such as time to angina, time to regression of angina, ischemic threshold and time to ST-segment normalization.

Table III shows the differences observed for the parameters just mentioned between the subchronic and the

TABLE III Differences Between Subchronic and Long-Term Trial

Exercise Variables	Time 0			4 Hours			12 Hours		
	D	DLt	Δ%	D	DLt	Δ%	D	DLt	Δ%
Duration	383 ± 108	386 ± 116	0.8	448 ± 127	427 ± 131	−4.7	420 ± 121	391 ± 110	−6.9
Time to AP	284 ± 92	295 ± 97	3.9	343 ± 105	324 ± 101	−5.5	319 ± 98	291 ± 87	−8.8
Time to APR	61 ± 16	74 ± 23	21.3*	68 ± 20	82 ± 27	20.6*	67 ± 18	74 ± 25	10.4*
Time to IT	291 ± 99	287 ± 94	−1.4	340 ± 114	303 ± 91	−10.9*	333 ± 111	286 ± 85	−14.1*
Time to STR	295 ± 124	297 ± 126	0.7	281 ± 119	305 ± 138	8.5	286 ± 114	289 ± 138	1.0

* $p \leq 0.05$.
Abbreviations as in Tables I and II.

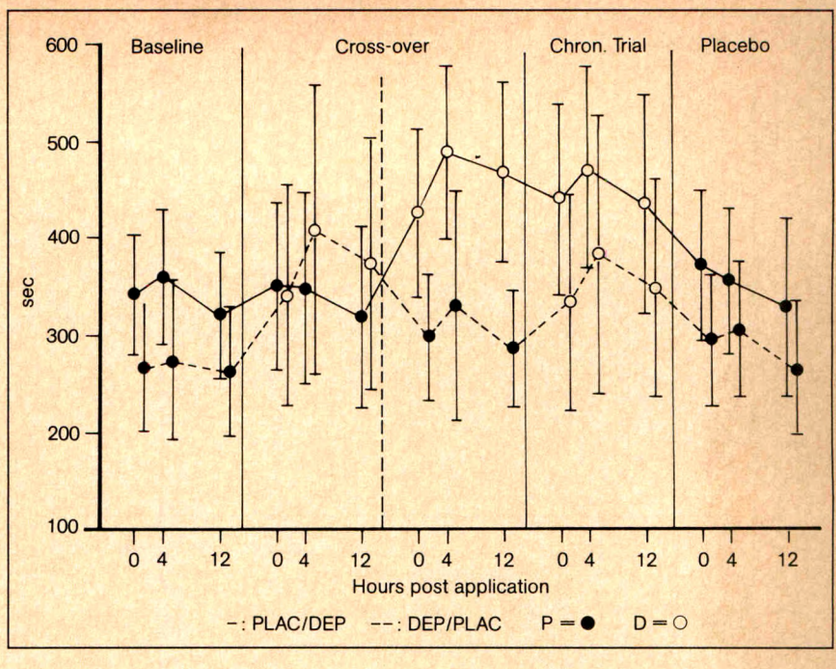


FIGURE 4. Maximal duration of exercise throughout the study period, at 0 time and 4 and 12 hours after application of patch. Baseline, after the first 7-day washout period; crossover 2-month period with the *vertical dotted line* which indicates the time of the crossover; chronic trial of 3 months with final evaluation; placebo, last washout period of 7 days. *Continuous line* means sequence placebo-Deponit; *dotted line* sequence Deponit-placebo: a significant improvement is observed during the treatment with active patch during both the subchronic and chronic phases, whereas the second washout period results are similar to the first period of washout and to placebo arm of crossover trial. Abbreviations as in Figure 2.

chronic part of the trial. Duration of exercise was slightly diminished after 3 months of treatment but this difference was not statistically significant. A significant decrease in effect was observed on ischemic threshold and time to regression of angina at 4 and 12 hours.

Figure 4 shows the pattern of exercise duration along the whole period of study: the active patch increases exercise duration during both the crossover and the chronic trial compared with baseline, placebo arm and final washout. A similar pattern is seen in Figure 5 in the time to angina pectoris. Finally, Figure 6 shows ST-segment depression at comparable load or stage: The active patch reduces ST-segment displacement during both the crossover and the chronic study compared with placebo.

DISCUSSION

The first part of this study (double-blind, placebo-controlled crossover) confirms previous results showing significant antianginal and anti-ischemic effects of Deponit-10 patch in patients with stable angina pectoris.[18,22] This finding is in agreement with other investigators using other NTG transdermal delivery systems.[15–17]

The second part of the trial seems to indicate that the antianginal effect remains constant throughout the 3

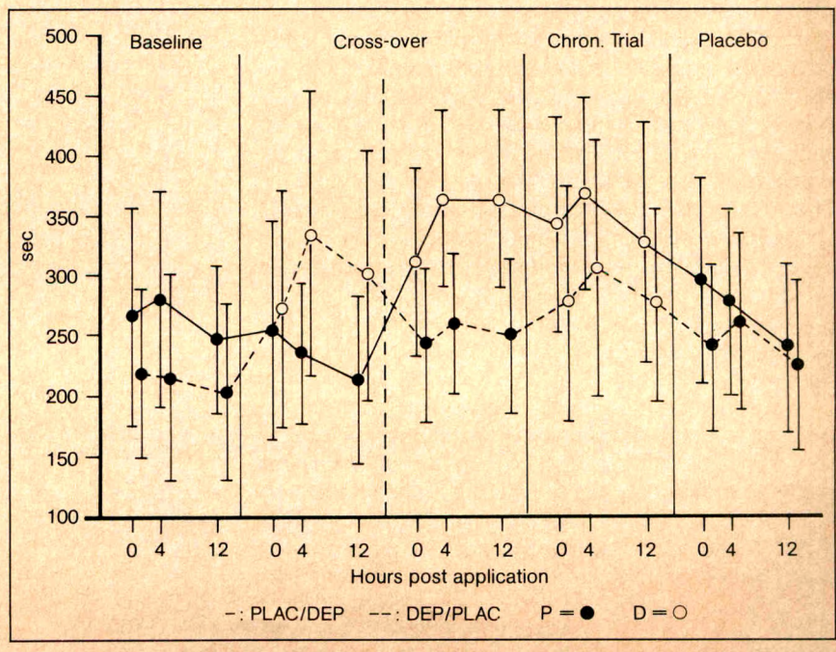


FIGURE 5. Time to onset of angina pectoris during exercise testing. A significant improvement is observed during active treatment with Deponit compared with placebo and both washout periods. Abbreviations as in Figure 2.

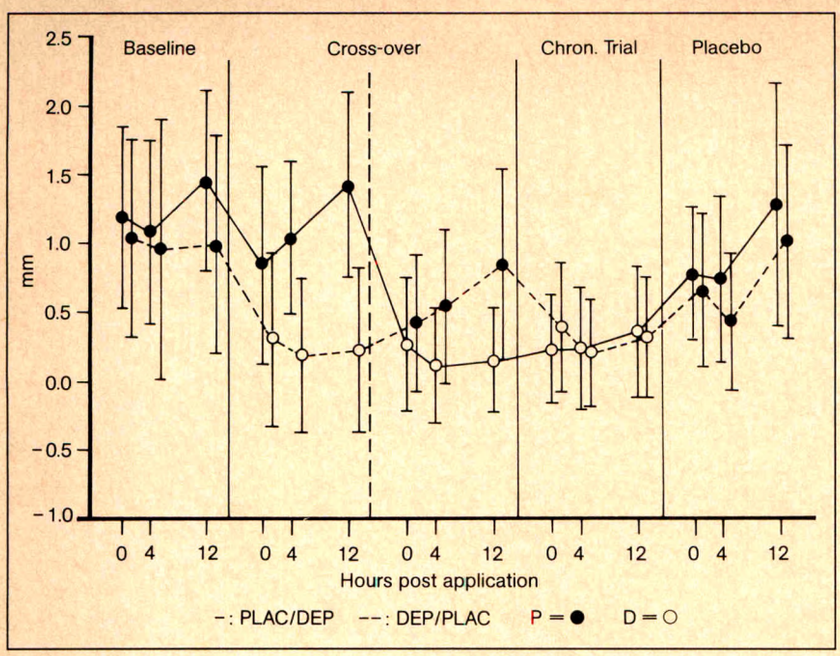


FIGURE 6. ST-segment depression at comparable stage or load. Considerable reduction of ST depression is observed during both subchronic and chronic trial compared with placebo and washout periods. Abbreviations as in Figure 2.

months of subchronic treatment and that this effect, although somewhat reduced, is also present after 3 months. Duration of exercise and time of onset of angina pectoris were slightly but not significantly reduced at the end of the chronic trial compared with the subchronic study. Time to regression of angina and to regression of ST-segment depression was significantly longer after long-term treatment compared with earlier results during the first part of the trial. These results show that some degree of attenuation of anti-ischemic effect has occurred but not to a degree that completely nullifies the therapeutic effects of the patch. The final washout period shows that persisting improvement was due to NTG patch and not to a training effect or to a spontaneous or pharmacologic (due to other drugs) improvement in the disease.

Our findings are in agreement with other workers who performed controlled subchronic and chronic studies using Deponit-10 or other NTG delivery systems,[13–18] but vary with findings of those who have shown rapid tolerance development with NTG patches and with other galenic preparations of nitrates in controlled studies.[5–11] This may explain the controversy that appears ongoing and relies on different patient selection, NTG preparations and different ways of dosage administration. Our patients were carefully selected among those who responded acutely to transdermal NTG patch to avoid considering tolerance which could have yielded no response from the start.

Another point that needs emphasis is that all of our patients were taking other drugs constantly throughout the study. Thus, association with other drugs, which often is the therapy of choice in the real clinical situation, may counterbalance the development of mechanisms contributing to tolerance development as has been seen with angiotensin-converting enzyme inhibitors combined with nitrates.[23] This association with other drugs may be a better alternative to a nitrate-free interval, an idea that has been proposed by several investigators to restore efficacy; however, it is limited to an incomplete therapeutic coverage during a 24-hour day.[11,12,24]

REFERENCES

1. Scheiner SL, Franton B, Yuan W, Sarkozy O, Johnson J, Gonscinsky L. Evaluation of Deponit a transdermal nitroglycerin film in the treatment of angina in clinical practice. *Curr Ther Res 1988;44:830–839.*

2. Tattersall AB, Dridgman KM, Obst D, Carr M. Retrospective post-marketing surveillance of transderm-nitro 5 in general practice in the United Kingdom. *J Int Med Res 1985;13:222–228.*

3. Hunter KW, Mahapatra R. Short term and chronic effects of transdermal nitroglycerin in stable angina pectoris. *Drug Develop Res 1986;9:219–224.*

4. Puech P. Evaluation sur cours d'une administration de long durèe (6 mois) de l'intéret thérapeutique d'une nouvelle form d'administration de trinitrine par voie transdermique dans l'angor d'effort. *Gazette Medicale 1987;94:8.*

5. Reichek N, Priest C, Zimrin D, Chandler T, St John Sutton M. Antianginal effects of nitroglycerin patches. *Am J Cardiol 1984;54:1–7.*

6. Parker JO, Fung HL. Transdermal nitroglycerin in angina pectoris. *Am J Cardiol 1984;54:471–476.*

7. Thadani U, Hamilton SF, Olson E, Anderson J, Vogles W, Prasad R, Teague SM. Transdermal nitroglycerin patches in angina pectoris. Dose titration, duration of effect and rapid tolerance. *Ann Intern Med 1986;105:485–492.*

8. Blasini R, Reininger G, Brugmann U. Tolerance to the anti-ischemic effect of isosorbide dinitrate during continuous but not during intermittent oral therapy. In: Cohn JN, Rittenhausen R, eds. Mononitrates. *Berlin: Springer-Verlag, 1985: 124–129.*

9. Silber S, Krause KH, Theisen K. Nitrate tolerance: dependence on dosage intervals (abstr)? *Circulation 1984;70:suppl II:II-189.*

10. Dalal JJ, Parker JO. Nitrate cross-tolerance: effect of sublingual isosorbide dinitrate and nitroglycerin during sustained nitrate therapy. *Am J Cardiol 1984;54:286–288.*

11. Parker JO, Fung HL, Ruggirello D, Stone JA. Tolerance to isosorbide dinitrate: rate of development and reversal. *Circulation 1983;68:1074–1080.*

12. Parker JO, Farrell B, Lahey KA, Moe G. Effect of intervals between doses on the development of tolerance to isosorbide dinitrate. *N Engl J Med 1987; 316:1440–1444.*

13. Franciosa JA, Cohn JN. Sustained hemodynamic effects without tolerance during long-term isosorbide dinitrate treatment in chronic left ventricular failure. *Am J Cardiol 1980;45:640–654.*

14. Rajfer SI, Demma FJ, Goldberg LI. Sustained beneficial hemodynamic responses to large doses of transdermal nitroglycerin in congestive heart failure and comparison with intravenous nitroglycerin. *Am J Cardiol 1984;54:120–125.*

15. Leier CV, Huss P, Magorien RD, Unverferth DV. Improved exercise capacity and differing arterial and venous tolerance during chronic isosorbide dinitrate therapy for congestive heart failure. *Circulation 1983;67:817–822.*
16. Muiesan G, Agabiti-Rosei E, Muiesan L, Romanelli G, Pollavini P, Pasotti C, Fiori G, Muratore L, Zuarini AM, Pastorini C, Bomiani S, Bozzi LB, Marchetti S. A multicenter trial of transdermal nitroglycerin in exercise-induced angina: individual antianginal response after repeated administration. *Am Heart J 1986;112:233–238.*
17. Scardi S, Pandullo C, Pivotti F, Ceschia G, Pollavini G. Individual responses to transdermal nitrates after chronic administration in angina pectoris. *Int J Cardiol 1988;21:21–32.*
18. Rezaković DE, Štalec J. Acute and chronic efficacy of 10 mg of nitroglycerin patch in stable angina pectoris. *Am J Cardiol 1988;61:52E–58E.*
19. Heepe W. Trandermales nitroglycerin (10 mg/24 std) in placebokontrollierten akutversuch und während einer offenen therapie über 12 monate bei stabiler angina pectoris. *Herz/Kreislauf 1987;19:suppl 1:30–33.*
20. Schneeweiss A, Marmor A. Transdermal nitroglycerin patches for silent myocardial ischemia during antianginal treatment. *Am J Cardiol 1988;61:36E–38E.*
21. Chatterjee K. Role of nitrates in silent myocardial ischemia. *Am J Cardiol 1987;60:18H–25H.*
22. Greco R, D'Alterio D, Schiattarella M, Boccia A, Greco L, Marsico F. Efficacy of a new transdermal nitroglycerin patch (Deponit 10) for stable angina pectoris. *Am J Cardiol 1988;61:44E–51E.*
23. Miller ED, Ackerly JA, Vaughan ED Jr, Peach MJ, Epstein RM. The renin-angiotension system during controlled hypotension with sodium nitroprusside. *Anesthesiology 1977;47:257–262.*
24. Rudolph W, Dirschinger J, Reiniger G, Beyerle A, Hall D. When does nitrate tolerance develop? What dosages and which intervals are necessary to ensure maintained effectiveness? *Eur Heart J 1988;9:suppl A:63–72.*

Interval Treatment of Coronary Artery Disease with Sustained-Release Isosorbide-5-Mononitrate

Wolfgang Jansen, MD, Regina Prenze, MD, Hartmut Kümper, MD, and Michael Tauchert, MD

The possibility of maintaining preload reduction and enhancement of exercise tolerance during an interval treatment with 50 mg/day of sustained-release isosorbide-5-nitrate (IS-5-N) was investigated in 13 patients (aged 54.4 ± 7.9 years [mean ± standard deviation]) with angiographically confirmed coronary artery disease and chronic stable angina pectoris. The effects of a single dose (acute test) were compared with those following an 8-day (chronic) regimen of mononitrate administration.

Two hours after administration of 50-mg sustained-release IS-5-N, mean resting pulmonary arterial pressure (PAP), measured with a Swan-Ganz catheter, was reduced by 27% ($p < 0.01$), and at submaximal exercise level (50 W, 3 minutes) by 34% ($p < 0.001$). At individually highest comparable work loads mean PAP was reduced by 28% ($p < 0.01$), and at maximal work load the PAP reduction was 21% ($p < 0.05$).

At the end of 1 week of therapy with sustained-release IS-5-N a slight, clinically irrelevant reduction of hemodynamic effects was recorded.

Work capacity increased after 1 hour by 60% (408 ± 104 vs 653 ± 147 W × min, $p < 0.001$)—still significantly above baseline 10 hours after nitrate administration. No difference from baseline was demonstrable 24 hours after medication. During interval therapy the improved work capacity was fully maintained (chronic, 1 hour: 417 ± 93 vs 679 ± 160 W × min, $p < 0.001$).

During interval therapy with sustained-release IS-5-N, hemodynamics and exercise tolerance were durably improved. Thus, the once-daily intake is beneficial for patient compliance and prevents tolerance development during long-term management of coronary artery disease.

(Am J Cardiol 1990;65:16J–22J)

Nitrates are used as basic medication in almost all patients with angina pectoris,[1] unless there are striking contraindications. Nitroglycerin remains the drug of first choice for alleviating acute or exercise-induced anginal attacks and it is superior in this respect to any other antianginal compound. For the long-term management of coronary artery disease, however, isosorbide dinitrate (ISDN) and isosorbide-5-nitrate (IS-5-N) are especially suitable.[2] After oral administration ISDN undergoes an extensive "first pass" metabolism in the liver, and thus mainly isosorbide-2-nitrate and IS-5-N are demonstrable in the plasma. In contrast, IS-5-N does not undergo a first-pass effect, and therefore because of its nearly 100% bioavailability, is most suitable for long-term management of coronary artery disease.[3]

However, because clinically relevant nitrate tolerance may develop during long-term nitrate therapy with high doses and brief dosing intervals, causing constantly elevated plasma concentrations[4,5] (together with intermittent low-dose nitrate therapy[6]), the once-daily administration of high-dose sustained-release ISDN and IS-5-N preparations gained increasing acceptance.[7–11] With the rhythmic circadian oscillations of plasma nitrate concentrations resulting from this so-called interval therapy the development of nitrate tolerance was to be averted and patient compliance essentially improved.[12]

The present investigation was aimed at assessing the hemodynamic and antianginal potency of 50-mg sustained-release IS-5-N after acute dosing in patients with angiographically confirmed coronary artery disease with the aid of standardized exercise, and at finding out whether any signs of tolerance development would occur at the end of 1 week of monotherapy with 50-mg sustained-release IS-5-N.

PATIENTS

Thirteen men with angiographically confirmed coronary artery disease, aged 41 to 65 years (mean 54.4 ± standard deviation 7.9) were included in the study. All patients had given informed consent to participate. All had stable angina pectoris. Patients with unstable angina pectoris, malignant arrhythmias, manifest heart failure, arterial hypertension requiring treatment, valvular disorders and pulmonary diseases were not included. Six of the patients had a history of myocardial infarction; 7 patients had 1-vessel, 4 had 2-vessel and the remaining patients 3-vessel disease. Ergometer stress testing for diagnosis was followed by a 3-day washout period during which the patients were not allowed to take antianginal drugs ex-

From the First Medical Department, City Hospital, Leverkusen, Federal Republic of Germany.

Address for reprints: Wolfgang Jansen, MD, First Medical Department, City Hospital, D-5090 Leverkusen 1, Federal Republic of Germany.

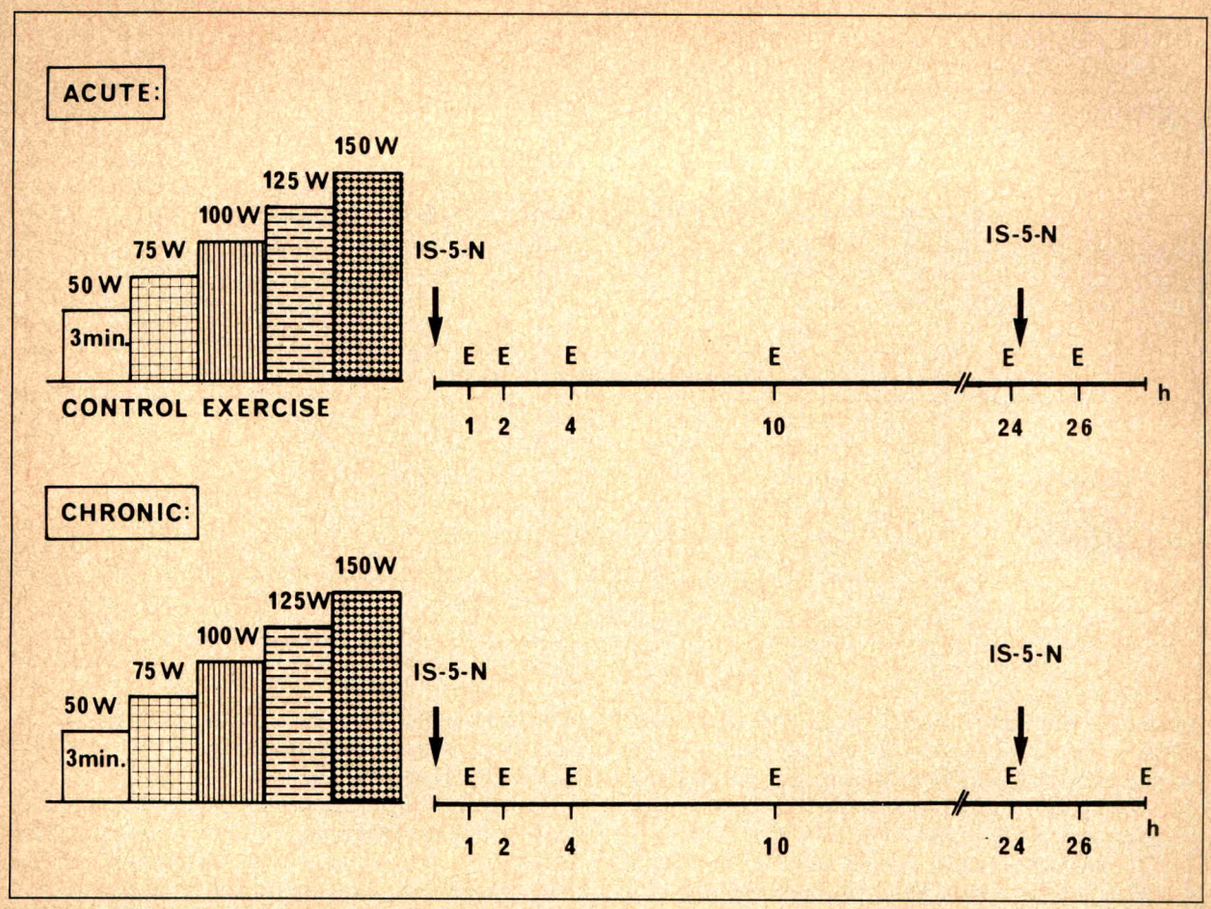


FIGURE 1. ***Top,*** **study protocol on day 1 and day 2. Baseline exercise test followed by administration of 50-mg sustained-release IS-5-N, and exercise tests after 1, 2, 4, 10 and 24 hours; repeated exercise 2 hours after 50-mg sustained-release IS-5-N (26 hours).** ***Bottom,*** **study protocol on day 8 after premedication exercise, administration of 50-mg sustained-release IS-5-N and repeat exercise tests after 1, 2, 4, 10 and 24 hours, as well as after administration of another 50-mg sustained-release IS-5-N (26 hours). E = exercise.**

cept for nitroglycerin capsules or spray for anginal attacks. At the conclusion of the washout period as well as after 1 week of therapy investigations were performed according to the trial protocol shown in Figure 1.

After inserting the Swan-Ganz catheter into the pulmonary circulation and after 15 minutes of adaptation to the diagnostic procedure, the following hemodynamic parameters were determined or calculated: heart rate (from electrocardiography), phasic and mean arterial pressure (cuff method), phasic or mean pulmonary artery pressure (PAP) (Flexopulmocath by Grandjean F4, Fr. Vygon, Aachen, Statham P23 ID), and pressure-rate product (systolic blood pressure × heart rate). After measurements were obtained at rest, supine bicycle exercise on a round-independent bicycle ergometer was performed at 50 W for 3 minutes. At the end of the third exercise minute (submaximal exercise) all parameters were determined; subsequently, exercise was continued at 25-W increments for 3 minutes each up to the symptom-limited work load (maximal exercise).

Maximal work capacity was calculated as the product of Watts × exercise duration in minutes.

The following inclusion criterion was selected for the study: increase of mean PAP to >30 mm Hg at the third minute on the 50-W exercise level.

Criteria for discontinuation were exercise dyspnea or anginal pains, peripheral exhaustion, increase of mean PAP to >60 mm Hg, pathologic blood pressure elevation to >230 mm Hg systolic or 130 mm Hg diastolic, and pathologic heart rate acceleration to >200 minus years of age.

After a 15-minute recovery phase during which all parameters returned to baseline values, every patient received an oral tablet containing 50-mg sustained-release IS-5-N. One and 2 hours later, respectively, all parameters were again measured according to the previously described protocol. Subsequently, the right-sided cardiac catheter was removed. Four, 10 and 24 hours after the first mononitrate dose, supine exercise was repeated. On the following day, 2 hours after the administration of 50-mg sustained-release IS-5-N (26th hour) supine exercise was again performed. Immediately afterward every patient was started on 1-week monotherapy with 1 daily dose of 50-mg sustained-release IS-5-N. No concomitant

TABLE I Effect of Acute (A) and One-Week Therapy (C) with 50 mg of Sustained-Release Isosorbide-5-Nitrate at Rest and at Submaximal Exercise (50 W, 3 Minutes)

Parameter		Baseline	1 Hour	2 Hours	4 Hours	10 Hours	24 Hours	26 Hours
				Rest				
HR (beats/min)	A	69 ± 17	70 ± 16	71 ± 17	76 ± 17	69 ± 19	73 ± 16	73 ± 14
	C	71 ± 17	75 ± 18	76 ± 18	77 ± 19	71 ± 14	72 ± 13	74 ± 15
$BP_s \times HR$ (mm Hg/min $\times 10^{-2}$)	A	89 ± 28	80 ± 23*	78 ± 23*	88 ± 21	86 ± 20	93 ± 25	87 ± 23
	C	90 ± 26	90 ± 25	88 ± 29	93 ± 30	89 ± 23	91 ± 24	91 ± 24
BP_{mean} (mm Hg)	A	98 ± 12	93 ± 13*	90 ± 9*	96 ± 9	96 ± 8	96 ± 8	92 ± 10
	C	98 ± 11	97 ± 10	94 ± 8	96 ± 10	98 ± 9	97 ± 9	93 ± 10
				Submaximal Exercise (50 W; 3 minutes)				
HR (beats/min)	A	105 ± 16	99 ± 15	101 ± 14	106 ± 14	102 ± 13	107 ± 16	103 ± 13
	C	108 ± 15	103 ± 16	104 ± 15	106 ± 15	107 ± 16	103 ± 17	102 ± 16
$BP_s \times HR$ (mm Hg/min $\times 10^{-2}$)	A	166 ± 40	151 ± 40*	151 ± 31*	159 ± 36	157 ± 27	163 ± 37	156 ± 31
	C	169 ± 36	158 ± 35	160 ± 38	166 ± 36	166 ± 40	158 ± 40	155 ± 34
BP_{mean} (mm Hg)	A	117 ± 13	111 ± 13	108 ± 13	106 ± 9	109 ± 10	108 ± 12	108 ± 13
	C	115 ± 11	114 ± 11	116 ± 13	113 ± 10	113 ± 10	110 ± 9	109 ± 8

* $p < 0.05$.
Values are mean ± standard deviation.
BP_{mean} = mean arterial pressure; $BP_s \times HR$ = pressure-rate product; HR = heart rate.

treatment with other coronary drugs, diuretic agents or digitalis was allowed except for nitroglycerin in case of anginal attacks. After 1 week of treatment, the previously described protocol of hemodynamic and ergometric parameters was repeated for every patient.

The Student *t* test for related samples was used for statistical comparisons. The significance level was fixed at a value of $p < 0.05$. The data were reported as mean ± standard deviation.

RESULTS

The 1-week monotherapy with 50-mg sustained-release IS-5-N was well tolerated by all of the patients. Because they had been formerly treated with various ISDN or IS-5-N doses, none complained of headaches.

Heart rate and arterial pressure: No significant increase in heart rate was recorded after the intake of 50-mg sustained-release IS-5-N either at rest or during submaximal exercise. At the end of the 1-week nitrate treatment there were no significant changes compared with baseline (Tables I and II).

With regard to mean arterial pressure, a significant decrease was recorded within 2 hours after acute nitrate intake, both at rest and during submaximal exercise. Four hours after nitrate administration as well as after the 1-week mononitrate therapy, no clinically relevant influence on systolic and mean arterial pressure was noted. Diastolic arterial pressure was not conclusively influenced by mononitrates either at rest or during exercise.

No significant difference in heart rate and arterial pressure was recorded during maximal exercise, both after acute and chronic mononitrate intake (Table II).

Pressure-rate product: In accordance with the systolic blood pressure reduction, the pressure-rate product significantly decreased both at rest and during submaximal exercise 1 and 2 hours after dosing, respectively. At

TABLE II Effect of Acute (A) and One-Week Therapy (C) with 50 mg of Sustained-Release Isosorbide-5-Nitrate per Day During Maximal Exercise Level (Discontinued)

Parameter		Baseline	1 Hour	2 Hours	4 Hours	10 Hours	24 Hours	26 Hours
				Maximal Exercise (Discontinued)				
HR (beats/min)	A	117 ± 20	127 ± 19	126 ± 18	125 ± 16	120 ± 18	115 ± 17	127 ± 16
	C	121 ± 16	131 ± 15	133 ± 15	130 ± 16	127 ± 14	118 ± 20	126 ± 15
$BP_s \times HR$ (mm Hg/min $\times 10^{-2}$)	A	200 ± 59	238 ± 69	238 ± 64	218 ± 48	212 ± 45	195 ± 48	237 ± 54
	C	208 ± 48	248 ± 52	248 ± 52	244 ± 41	230 ± 38	204 ± 52	238 ± 37
BP_{mean} (mm Hg)	A	122 ± 16	126 ± 15	126 ± 14	118 ± 12	120 ± 14	117 ± 13	124 ± 12
	C	124 ± 12	129 ± 13	129 ± 11	127 ± 9	127 ± 11	119 ± 10	127 ± 9
Working capacity (W × min)	A	408 ± 104	653 ± 147*	669 ± 151*	587 ± 129*	524 ± 81*	379 ± 84	646 ± 114*
	C	417 ± 93	679 ± 160†	708 ± 125†	631 ± 125†	534 ± 124†	413 ± 157	673 ± 101†
Duration of exercise (sec)	A	374 ± 77	522 ± 78*	533 ± 89*	485 ± 79*	445 ± 55*	355 ± 60	519 ± 63*
	C	382 ± 63	530 ± 86*	554 ± 69*	522 ± 63†	460 ± 67*	373 ± 101	554 ± 95†

* $p < 0.01$; † $p < 0.001$.
Values are expressed as mean ± standard deviation.
Abbreviations as in Table I.

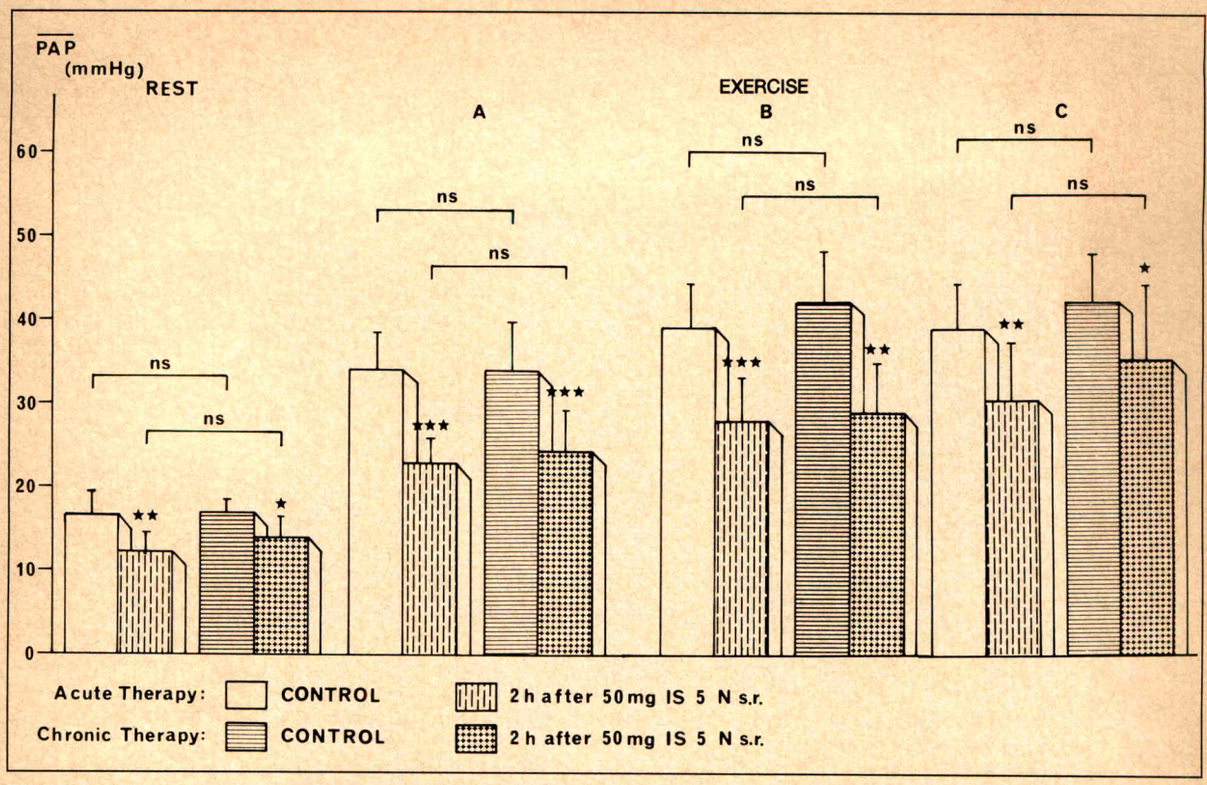


FIGURE 2. Mean pulmonary artery pressure (PAP) before and 2 hours after 1 week of treatment with daily 50-mg sustained-release (s.r.) IS-5-N in 13 patients with coronary artery disease (A = 50 W, 3 min; B = individually highest comparable exercise level; C = maximal exercise [discontinued]). ns = nonsignificant; *p <0.05; **p <0.01; ***p <0.001); values are mean ± standard deviation.

no time throughout chronic mononitrate administration were conclusive changes of this parameter recorded (Tables I and II).

Pulmonary artery pressure: One and 2 hours after the administration of 50-mg sustained-release IS-5-N, the resting mean PAP decreased 31% ($p < 0.01$) and 27%, respectively ($p < 0.01$). At the end of the 1-week monotherapy there was no difference from baseline values (16.8 ± 3.1 mm Hg vs 16.6 ± 1.4 mm Hg). After another dose of 50-mg sustained-release IS-5-N, PAP was reduced only 11% during the first and second hour. At submaximal exercise mean PAP was reduced 34% ($p < 0.001$) after 1 and 2 hours compared with control values (Table II, Fig. 2).

At individually highest comparable exercise levels before and after nitrate administration, PAP reductions after 1 and 2 hours, respectively, were 28% ($p < 0.001$). During maximal exercise (discontinued before and after nitrate administration), PAP after 1 and 2 hours was below baseline values by 21% ($p < 0.01$).

At the conclusion of the 1-week monotherapy, PAP reductions during submaximal exercise (first and second hour) was 26% ($p < 0.001$) and 29%, respectively, ($p < 0.001$); at individually highest comparable exercise levels (first and second hour), reduction was 19% ($p < 0.01$) and 29% ($p < 0.001$), respectively; during maximal exercise (discontinued) (first and second hour), reduction was 15% ($p < 0.05$) (Table III, Fig. 2).

TABLE III Effect of Acute (A) and One-Week Treatment (C) with 50 mg of Sustained-Release Isosorbide-5-Nitrate per Day on Mean Pulmonary Artery Pressure at Rest, at Submaximal Exercise Level (50 W, 3 Minutes), at Individually Highest Comparable Exercise Level and During Maximal Exercise (Discontinued)

PAP mean (mm Hg)		Baseline	1 Hour	2 Hours
Rest	A	16.8 ± 3.1	11.6 ± 2.4†	12.3 ± 2.1†
	C	16.6 ± 1.4	14.7 ± 1.3*	14.7 ± 2.3*
Submaximal exercise (50 W 3 min)	A	34.0 ± 4.4	22.5 ± 5.0‡	22.8 ± 2.9‡
	C	34.1 ± 6.0	25.2 ± 4.3‡	24.4 ± 5.0‡
Indiv. highest comparable exercise level	A	39.1 ± 5.2	28.0 ± 6.6†	27.9 ± 5.3‡
	C	41.4 ± 5.7	33.1 ± 6.2†	29.0 ± 5.9†
Max. exercise (discontinued)	A	39.1 ± 5.2	31.8 ± 7.2†	30.9 ± 7.1†
	C	41.4 ± 5.7	36.6 ± 7.9*	35.3 ± 8.9*

* $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$.
Indiv. = individually; Max. = maximal; PAP = pulmonary artery pressure.

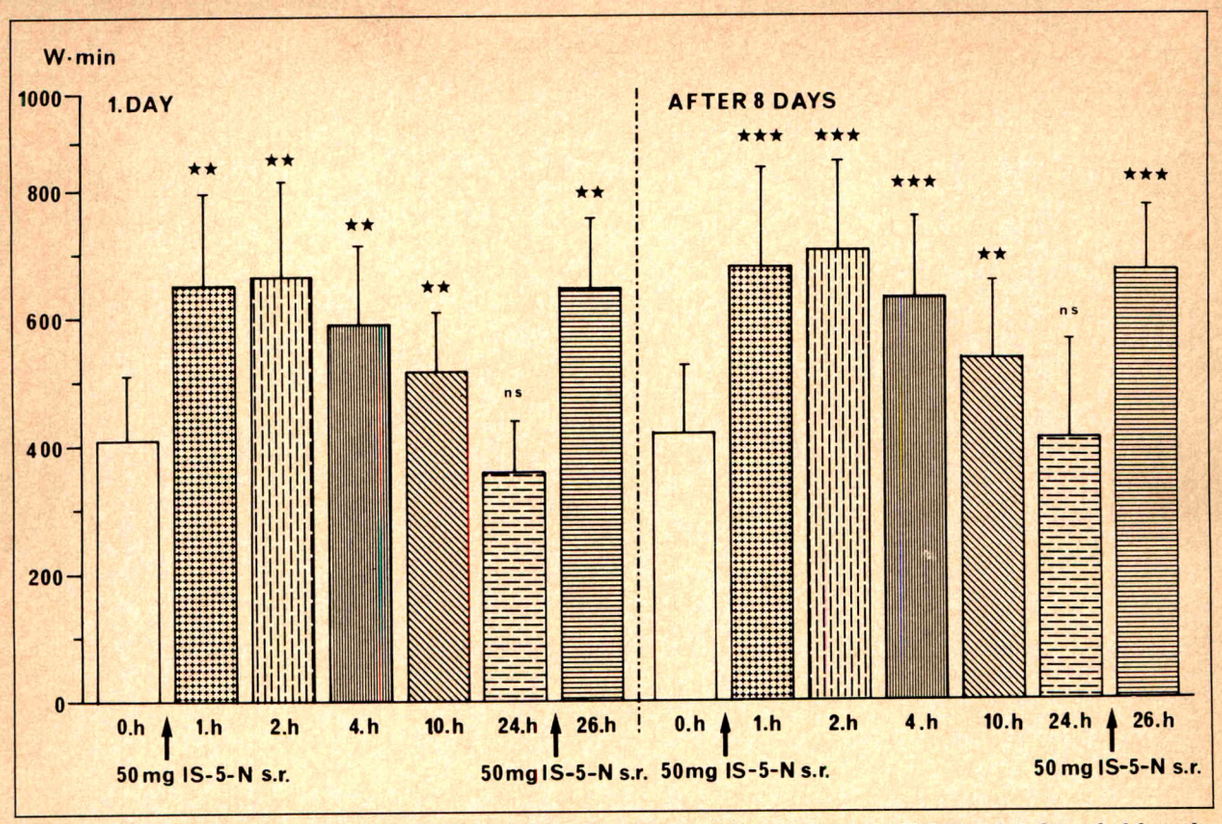


FIGURE 3. Working capacity (W × min) after acute dosing with 50-mg sustained-release (s.r.) IS-5-N and at the end of 1-week monotherapy with daily 50-mg sustained-release IS-5-N in 13 patients with coronary artery disease. ns = nonsignificant; **p <0.01; ***p <0.001; values are mean ± standard deviation.

Work capacity and work load: During the first and second hours after 50-mg sustained-release IS-5-N, work capacity increased 60 and 63%, respectively (both p <0.001). The increased work capacity after single-dose medication was still present 4 (44%, p <0.01) and 10 (28%, p <0.01) hours later; after 24 hours, however, there was no longer a difference from the initial value (379 ± 84 vs 408 ± 104 W × min). Two hours after another dose of mononitrate (26 hours) it increased again, as on the previous day, to 646 ± 114 W × min (p <0.01) (Table II, Fig. 3).

At the conclusion of the 1-week monotherapy with 50 mg/day sustained-release IS-5-N, the initial value of work capacity was not different from the baseline (408 ± 104 vs 417 ± 93 W × min). However, 1 hour after administration of 50-mg sustained-release IS-5-N, it was 679 ± 160 W × min (63%, p <0.001). Two, 4 and 10 hours afterward, work capacity was significantly enhanced by 70% (p <0.001), 51% (p <0.001), and 38% (p <0.01), respectively, above the initial value, whereas no increase was demonstrable 24 hours later. As on the second day, work capacity increased on the ninth day by 63%, from 413 ± 157 to 673 ± 101 W × min 2 hours after mononitrate administration (Table II, Fig. 3).

Exercise duration was significantly prolonged for 10 hours by 50-mg sustained-release IS-5-N (first hour, 40%; second hour, 43%; fourth hour, 30%; and tenth hour, 19%). No tapering of the effect was demonstrable after 1 week of daily dosing with 50 mg sustained-release IS-5-N compared with the initial values (Table II, Fig. 4).

DISCUSSION

Efforts to reduce the number of daily antianginal tablets in order to benefit the patients and to improve their compliance have resulted in the development of high-dose sustained-release nitrate formulations. These preparations were intended to afford antianginal protection for 10 to 12 hours after a single dose in the morning on the one hand, and to prevent the build-up of high plasma concentrations on the other, i.e., nitrate accumulation that may lead to nitrate tolerance.[13–16]

Our results confirmed the clear-cut, preload-reducing and antianginal short-term effects of 50-mg sustained-release IS-5-N in patients with coronary artery disease. The antianginal effect starts within 30 minutes and is most pronounced after 2 hours. The prolongation of the time to exercise-induced angina pectoris lasts for >10 hours, and is no longer demonstrable 24 hours after mononitrate administration.

During 1 week of monotherapy with 50-mg sustained-release IS-5-N, no tapering of the antianginal effects was noted, and the improvement in exercise tolerance remained unchanged. In all patients, there was a marked reduction of PAP 1 and 2 hours after the first dose of 50-

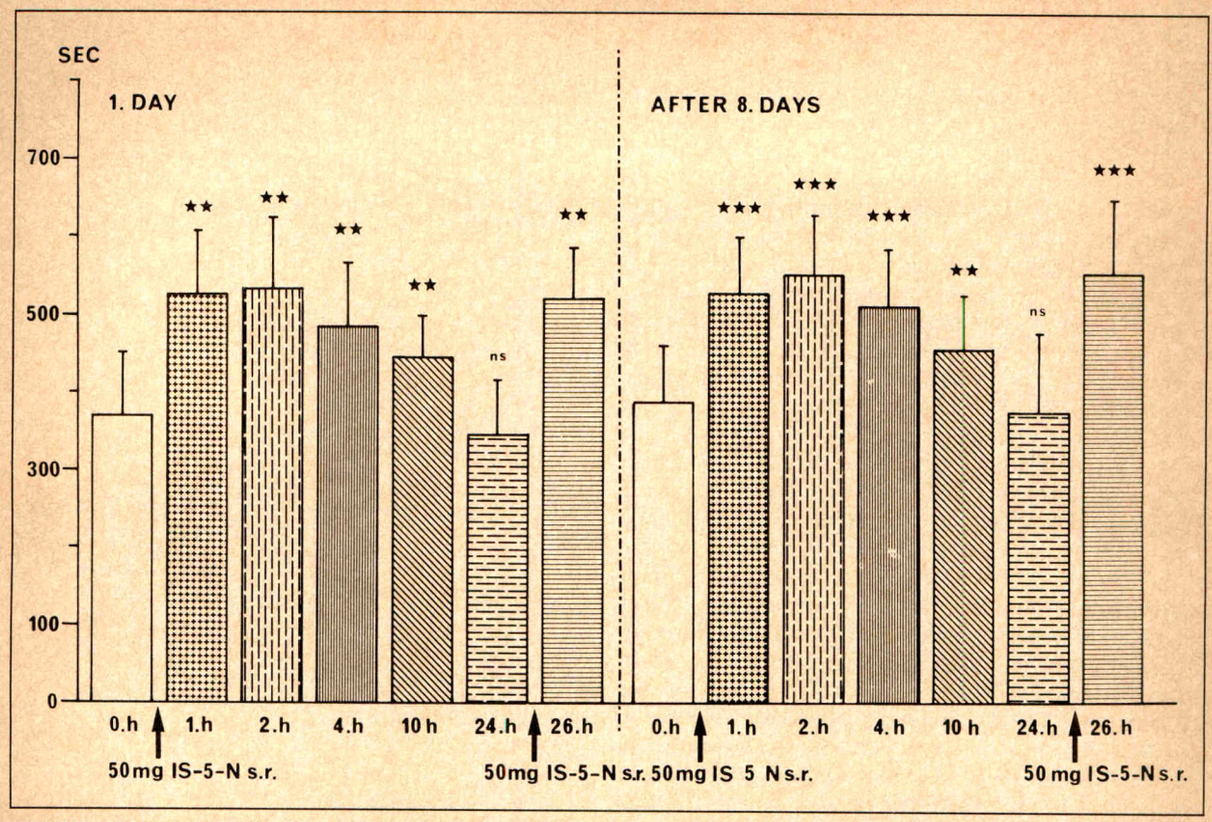


FIGURE 4. Exercise duration (sec) after acute dosing with 50 mg sustained-release (s.r.) IS-5-N and after 1 week of monotherapy with daily 50-mg sustained-release IS-5-N in 13 patients with coronary artery disease. ns = nonsignificant; **p <0.01; ***p <0.001); values are mean ± standard deviation.

mg sustained-release IS-5-N, and this reduction was especially pronounced during exercise. After 1 week of nitrate therapy, measurements of PAP revealed a slight, clinically nonrelevant regression of preload reduction.

Our findings agree with those of other groups who used high-dose preparations of ISDN or IS-5-N in sustained-release formulation. Thus, after the first dose of 120-mg sustained-release ISDN as well as after 1 to 4 weeks of continuous monotherapy, most of the groups reported anti-ischemic protection and an increase in exercise capacity lasting 10 to 12 hours. No group observed a sufficiently pronounced antianginal and anti-ischemic effect after 24 hours.[7–10,12,17–20] Using interval therapy with various sustained-release formulations of IS-5-N, Ansmann and Schirmer,[20] Eggeling et al,[21] Kenedi[22] and Mitrovic et al[23] equally found anti-ischemic protection and significant increases in exercise tolerance lasting for >8 hours. This 24-hour interval therapy with 50-mg sustained-release IS-5-N also showed no demonstrable improvement in exercise tolerance after 24 hours. In contrast to the findings of these investigators and to our own, only Bramann et al[24] demonstrated a persistent improvement in exercise tolerance 24 hours after administration of 40-mg sustained-release IS-5-N.

Although our group unequivocally confirmed the effectiveness of 24-hour interval therapy with 50-mg sustained-release IS-5-N based on hemodynamic measurements and repeated exercise testing, Thadani et al[25] reported the development of complete hemodynamic and antianginal tolerance after 1 week of treatment with 50- and 100-mg sustained-release IS-5-N. Four hours after the first dose of 50- or 100-mg sustained-release IS-5-N, they noted a significant acceleration in heart rate by 9 and 11% and a prolongation of exercise time of 17 and 22%. These parameters, however, were no longer distinguishable from their baseline values 20 and 24 hours after acute dosing. After 1 week of monotherapy, 4 hours after a new dose of sustained-release IS-5-N, no significant increase in heart rate and exercise duration occurred, despite plasma concentrations that were about the same during chronic treatment as after acute dosing.

This pronounced tolerance development during interval therapy was not confirmed so far by any other group of investigators using either ISDN or IS-5-N in sustained-release formulations. Unlike the Thadani protocol, our investigations as well as the study by Wortmann et al[18] were conducted according to an open design without placebo control for ethical reasons. This was possible because we,[26] in accordance with the group of Khurmi et al,[27] were able to demonstrate that placebo does not have an essential influence on hemodynamics and work capacity. Thadani explained tolerance development during chronic interval therapy with sustained-release IS-5-N by

high plasma concentrations of 2- and 5-mononitrate, respectively. This was at variance with the findings of our group which failed to observe a reduction in either hemodynamic or antianginal effects even after 1 week of treatment with 100-mg sustained-release IS-5-N, although 24 hours after nitrate administration IS-5-N plasma concentrations of >200 ng/ml were measured.[28]

Because of the circadian oscillation of plasma nitrate concentrations, the investigated therapeutic schedule of once-daily 50-mg sustained-release IS-5-N corresponds to a 24-hour interval therapy. Tolerance development may be prevented by intermittent nitrate administration and the resulting plasma concentration changes. The antianginal and anti-ischemic nitrate effects are thus fully preserved during long-term treatment. After the morning dose of 50-mg sustained-release IS-5-N, the patients are sufficiently protected for the duration of their physical activity. For these patients, a 24-hour interval treatment with high-dose nitrate preparations is more suitable than a 12-hour dosing interval, because the antianginal and the anti-ischemic protection is clearly diminishing 6 to 8 hours after intake of low-dose nitrates in normal formulation.[6,29] At the same time, the concept of interval therapy contributes toward improving patient compliance. The use of this sustained-release formulation for the treatment of coronary artery disease is justified by a good tolerability of the investigated substance and its prolonged antianginal effectiveness lasting for >10 hours. Thus, neither transdermally applied nitroglycerin[30] nor ISDN[31] nor high-dose ISDN or IS-5-N sustained-release preparations[7,10,28] is able to afford antianginal and anti-ischemic protection around the clock, i.e., for 24 hours. Therefore, whenever required by the clinical condition and provided there are no contraindications, combined therapy with nitrate and β-receptor blocking agents or, respectively, nitrates and calcium antagonists should be considered for long-term therapy.[32]

REFERENCES

1. Strauer BE. Pathophysiologische und pharmakologische Grundlagen der Therapie der koronaren Herzkrankheit. *Internist 1987;28:711–720.*

2. Noack E. Pharmakologische Basis für die Therapie mit organischen Nitraten. *Herz 1982;7:275–82.*

3. Abshagen U, Betzien G, Enderle R, Kaufmann B, Neugebauer G. Pharmacokinetics and metabolism of isosorbide-dinitrate after intravenous and oral administration. *Eur J Clin Phamacol 1985;27:637–644.*

4. Blasini R, Rieniger G, Rudolph W. Vermeidung einer Toleranzentwicklung bei Langzeittherapie mit Nitraten durch korrekte Dosierung. *Z Kardiol 1986;75: suppl 3:42–49.*

5. Parker JO. Nitrate tolerance. *Herz 1984;9:137–145.*

6. Jansen W, Osterpey A, Metternich M, Weste S, Hombach V, Fuchs M, Tauchert M, Hilger HH. Failing development of nitrate tolerance on chronic treatment with isosorbide dinitrate and isosorbide-5-nitrate. *Herz Kreislauf 1983;15:338–353.*

7. Blasini R, Brügmann U, Reiniger G, Rudolph W. Langzeittherapie der Belastungs-Angina-pectoris durch einmalige tägliche Verabreichung von 120 mg Isosorbiddinitrat in retardierter Form. *Herz 1985;10:163–171.*

8. Nyber G, Carlens P, Lindström E, Lundmann T, Nordlander R, Rehnquist N, Ulvenstam G, Aberg A, Aström H. The effect of isosorbide-5-mononitrate Duriles® on exercise tolerance in patients with exertional angina pectoris. A placebo controlled study. *Eur Heart J 1986;7:835–839.*

9. Wrobel N, Thalhofer S, Kiwus U. Hemodynamics and antiischaemic effects of single and maintenance dose of 60 mg slow release isosorbide-5-mononitrate in survivors of myocardial infarction. *Herz Kreislauf 1989;21:179–185.*

10. Ohlmeier H, Mertens HM, Möller M, Mannebach M, Gleichmann U. Vereinfachte Langzeittherapie der koronaren Herzkrankheit mit 120 mg retardiertem Isosorbiddinitrat einmal täglich. Untersuchung zu Wirkdauer und Toleranzwirkung. *Z. Kardiol 1986;75:suppl 3:50–56.*

11. Silber S. Clinical relevance of nitrate tolerance. In: Cohn JN, Rittinghausen R, ed. Mononitrates. *Berlin, Heidelberg, New York: Springer, 1984:130–146.*

12. Silber S. Can the problem of nitrate tolerance be solved? *Z Kardiol 1985;suppl 1:51–54.*

13. Boertz A, Bonn R. Nitrate therapy without loss of action by correct dosage. *Z Kardiol 1986;75:suppl 3:57–60.*

14. Luckow V, Jansen W, Osterpey A. Pharmakokinetik von Isosorbid-5-Nitrat nach Gabe einer neuartigen Retardformulierung. *Herz/Kreislauf 1984;17: suppl:127–134.*

15. Ingendaay A, Klein G, Rehm KD, Töberich H, Vanscheidt W. Vergleichende Pharmakokinetik retardierter Mononitrat-präparate. *Münch Med Wschr 1987; 129:34–36.*

16. Silber S. Retardierte Nitratformen. *Dtsch Med Wschr 1985;110:776–777.*

17. Wolff R, Nötges A, Traber U. Hemodynamic effects of a subchronic therapy with 120 mg ISDN in slow-release-form in patients with left heart failure. *Z Kardiol 1989;78:suppl 2:137–141.*

18. Wortmann A, Bachmann K, Deuber HJ, Roth E. Hämodynamik und Koronardynamik unter ISDN-Langzeittherapie. *Z Kardiol 1986;75:suppl 3:68–76.*

19. Bauer U, Morr Th, Eslami I, Wisotzki R. Akut- und Langzeitwirkung von Isosorbid-5-Nitrate in Retardform (abstr). *Z Kardiol 1985;74:suppl 5:84.*

20. Ansmann E, Schirmer G. Keine Toleranzentwicklung bei der antianginösen Therapie mit retardiertem Isosorbid-5-Nitrat. *Med Welt 1988;39:1141–1143.*

21. Eggeling T, Jansen W, Osterspey A, Tauchert M. Einfluss von 50 mg Isosorbid-5-Nitrat auf die Belastbarkeit von Patienten mit koronarer Herzkrankheit. *Med Klinik 1986;81:275–280.*

22. Kenedi P. Intraindividuelle Dosiswirkungsbeziehung von Elantan-long. *Z Kardiol 1986;75:suppl 3:77–79.*

23. Mitrovic V, Hain P, Bahawar H, Kornecki P, Volz M, Gessner C, Schlepper M. Correlation of the pharmacokinetics and the neurohumoral effects of a slow-release preparation of isosorbide-5-mononitrate after a 7-day-therapy and pharmacokinetics of the neurohumoral system after administration of 60 mg isosorbide-5-mononitrate in patients with coronary heart disease. *Herz/Kreislauf 1988;20:466–474.*

24. Bramann H, Grosse-Heitmeyer W, Wisotzki R. 24-h-Wirkungsprofil von 60 mg Isosorbid-Mononitrate Bei Patienten mit koronarer Herzkrankheit. *Med Welt 1987;38:1248–1252.*

25. Thadani U, Hamilton SF, Olson E, Anderson JL, Prasad R, Voyles W, Doyle R, Kirsten E, Teague SM. Duration of effects and tolerance of slow-release isosorbide-5-mononitrate for angina pectoris. *Am J Cardiol 1987;59:756–762.*

26. Jansen W, Behnke M, Osterspey A, Tauchert M. Reproducibility of haemodynamic parameters during exercise test in patients with coronary heart disease. *Herz/Kreislauf 1985;17:529–539.*

27. Khurmi NS, Raferty EB. Lack of diurnal variation on maximal symptom-limits exercise test response in chronic stable angina. *Am J Cardiol 1988;61:38–42.*

28. Rappert B, Jansen W, Prenzel R, Tauchert M. Mononitrat in Retardform: Kein Anhalt für eine Toleranz-entwicklung bei Intervalltherapie der Koronarinsuffizienz (abstr). *Acta Medica Austriaca 1989;16:63.*

29. Wortmann A, Bachmann K, Meinhold M. Intervall-Dauertherapie der koronaren Herzkrankheit mit Nitraten. *Therapiewoche 1988;38:3803–3809.*

30. Rieniger G, Kraus F, Dirschinger J, Blasini R, Rudolph W. Hochdosierte transdermale Nitroglyzerintherapie: Wirkungsverlust innerhalb von 24 Stunden. *Herz 1985;10:305–311.*

31. Parker JO, Vankoughnett KA, Fung HL. Transdermal isosorbide dinitrate in angina pectoris. Effect of acute and sustained therapy. *Am J Cardiol 1985;54:8–13.*

32. Silber S. Kombination antiangiöser Medikamente. *Z Kardiol 1989;78:suppl 2:160–174.*

Nitrate Therapy in the Elderly

Joseph S. Alpert, MD

Changes in the heart and blood vessels with age alter the response of the cardiovascular system to pharmacologic agents. Nitrate plasma half-life is longer and volume of distribution is larger in older persons. Apparently, these pharmacokinetic differences in older persons lead to increased venous smooth muscle responsivity to nitrates which, in turn, leads to greater reductions in central venous and pulmonary arterial pressures after nitrate administration. This is probably the explanation for the greater frequency of nitrate-induced severe hypotension and bradycardia in elderly patients with myocardial infarction compared with younger patients. Clinicians should be cognizant of the changes in the cardiovascular system which occur with age that sensitize the elderly patient to the action of organic nitrates. Initial dosages of nitrates should accordingly be less than in younger patients.
(Am J Cardiol 1990;65:23J–27J)

From the Division of Cardiovascular Medicine, University of Massachusetts Medical School, Worcester, Massachusetts.

Address for reprints: Joseph S. Alpert, MD, Division of Cardiovascular Medicine, University of Massachusetts Medical School, Worcester, Massachusetts 01655.

Cardiovascular disease occurs often in elderly patients. The diagnosis and management of a variety of cardiovascular conditions is often different in elderly subjects compared with younger patients. Changes with age in the cardiovascular system, liver and kidneys result in altered responses, distribution and metabolism of many cardiac drugs. Consequently, it is appropriate to review various aspects of cardiovascular disease in the elderly that differentiate these conditions from similar pathologic entities in younger patients. The major emphasis in this review will be on nitrate therapy in elderly patients with heart disease, particularly coronary artery disease.

THE AGING CARDIOVASCULAR SYSTEM

A number of changes occur in the cardiovascular system with aging. There are effects on both the heart and the blood vessels. The inherent rhythmicity of the sinoatrial node declines with age leading to a lessened heart rate response to exercise or other demands.[1] Similarly, maximal cardiac output decreases with age.

A variety of anatomic changes take place in the cardiovascular system with normal aging. Some of these changes increase the elderly patient's susceptibility to orthostatic or drug-induced hypotension (Table I). The left ventricular myocardium hypertrophies, probably in response to increasing systolic blood pressure which, in turn, is the result of decreasing arterial compliance and abnormal ventricular-vascular coupling.[2,3] Decreased left ventricular compliance increases the tendency for cardiac output to decrease in response to decreases in venous return which might occur with the administration of a venodilator. Age-associated changes in vascular connective tissue result in progressively increasing stiffness of the myocardium and arteries. The etiology of these changes in myocardial or arterial wall stiffness remains unknown. However, changes in arterial wall stiffness may be the result of increased collagen, elastin, glycosaminoglycans, calcium and lipid in the arterial walls of elderly patients.

In addition, the response of the heart to β-adrenergic stimulation diminishes with age, perhaps secondary to decreased numbers of β receptors in elderly subjects.[4] Thus, the older person's response to exercise resembles that of a younger person who has taken β blockers.

Because nitroglycerin acts on blood vessels, one should examine in more detail the effect of aging on vascular function (Table I). As noted earlier, advancing age is associated with decreased vascular distensibility of major arteries. In most developed countries, this loss of distensibility is associated with the development of systolic arterial hypertension.[3,5] Diastolic blood pressure usually remains normal. A second explanation for the observed

TABLE I Factors Predisposing Elderly Subjects to Orthostatic and Vasodilator-Induced Hypotension

Decreased vascular distensibility
Decreased myocardial compliance: increased sensitivity of cardiac output to decreased venous return
Decreased β-adrenergic response of the myocardium
Abnormal baroreceptor function: decreased response to arterial hypotension
Decreased extracellular fluid volume: decreased plasma volume

TABLE II Changes in Body Composition and the Physiology of Drug Metabolism with Age

Decreased total body water
Decreased plasma volume
Decreased lean body mass: increased percent body fat
Decreased serum albumin concentration
Decreased cardiac output: decreased hepatic blood flow
Decreased inducibility of hepatic enzymes
Decreased glomerular filtration rate

Adapted from *Am J Cardiol.*[10]

frequency of systolic hypertension in the elderly is an abnormal coupling of left ventricular function to arterial capacity so that too much blood is delivered from the left ventricle into the aorta during each systole.[2] This may be the result of excessive sympathetic nerve activity.

Elderly subjects frequently have abnormal arterial baroreceptor function. Thus, increases in heart rate with hypotension and bradycardia in response to hypertension are both blunted in the elderly.[6,7] Recently Amorim et al[8] tested autonomic nervous system function in healthy elderly male subjects.[8] They had decreased heart rate and arterial blood pressure responses to standardized stimuli, e.g., Valsalva maneuver, cold pressor test, intravenous infusion of phenylephrine, and so forth. Their results suggested decreased vagal function in these subjects. They also observed decreased sympathetic nervous stimulation of the heart with induced hypotension, as previously mentioned. It has been suggested that this abnormal baroreceptor function in the elderly is the result of altered arterial wall compliance.[5] Clearly, abnormal baroreceptor function coupled with decreased arterial compliance predispose older patients to orthostatic or drug-induced hypotension (Table I). It is important to bear this in mind when considering vasodilator therapy in these patients. Older persons have significantly less body water, especially in the extracellular compartment. Plasma volume is also decreased in geriatric patients.[9] This also helps to explain the greater susceptibility of older subjects to dehydration and orthostatic or drug-induced hypotension.

ALTERED DRUG PHARMACODYNAMICS IN THE ELDERLY

Adverse drug reactions are very common in older patients.[10] These reactions are the result of (1) altered patterns of drug distribution and metabolism in the elderly; (2) increased sensitivity to drug action in older subjects; and (3) the effect of disease and aging on organ function.[10]

Many changes occur in bodily composition and the physiology of drug metabolism in older persons (Table II). Thus, decreased total body water and plasma volume alter the volume of distribution of a particular agent, thereby shifting its tissue level and its rate of elimination. Lipid soluble drugs find increased body fat in older subjects, which also alters the volume of distribution. Decreased hepatic blood flow, hepatic enzyme inducibility and glomerular filtration rate decrease drug metabolism and clearance. The elimination rate of a drug from the body is a function of volume of distribution and clearance. As just noted, both of these variables are altered (often decreased) by aging. Therefore, the elimination rate for many drugs is decreased in geriatric patients.

Altered susceptibility to drug action is common in elderly persons. For example, the decreased response to β-adrenoreceptor stimulation and the alterations in baroreceptor function that occur in older subjects make them less sensitive to β-blocking agents.

Finally, and perhaps most important, elderly subjects are prone to a variety of degenerative, metabolic and neoplastic processes. Many of these pathologic states either alter drug metabolism or change individual susceptibility to drug action. For example, vasodilator drugs may alter perfusion/ventilation balance in the lung and thereby lead to arterial hypoxemia secondary to shunting of desaturated blood through the pulmonary vascular bed. Patients with chronic obstructive lung disease who are already desaturated may therefore tolerate vasodilator therapy poorly.

Despite the presence in elderly patients of the factors just discussed, many drugs may be administered to older subjects adhering to a dose and schedule similar to that used for younger persons. While some agents (e.g., heparin, benzodiazepines) do demonstrate age-related increases in toxicity, many compounds do not.[11] Furthermore, limited information is available for most drugs concerning age-related changes in distribution, metabolism and toxicity. The clinician must therefore exercise caution and common sense in prescribing for geriatric patients.

OVERVIEW OF NITRATE CLINICAL PHARMACOLOGY

A considerable body of information exists concerning the clinical pharmacology of organic nitrates. Much of this information has been obtained in animal models and younger patients. A general overview of these data follows.

Organic nitrates (nitroglycerin, isosorbide mononitrate and dinitrate and others) are potent relaxers of smooth muscle. They have a powerful effect on vascular smooth muscle with less effect on bronchiolar, gastrointestinal, ureteral and uterine smooth muscle. Nitrates relax both venous and arterial smooth muscle. Low concentrations of these agents produce predominantly venous dilatation, whereas higher concentrations dilate both arteries and veins.[12,13]

Venous dilatation pools blood in the periphery leading to a decrease in venous return, central blood volume, and ventricular filling volumes and pressures. Cardiac output

may remain unchanged or it may decline as a result of the decrease in venous return. Arterial blood pressure usually declines secondary to a decrease in cardiac output or arteriolar vasodilatation, or both. A modest reflex increase in heart rate results from the decrease in arterial blood pressure. Nitrates can dilate epicardial coronary arteries including atherosclerotic stenoses.[14]

The cellular mechanism of nitrate-induced smooth muscle relaxation has become apparent in recent years.[15–17] Nitrates enter the smooth muscle cell and are cleaved to inorganic nitrate and eventually to nitric oxide. This cleavage requires the presence of sulfhydryl groups which apparently come from the amino acid, cysteine.[17] Nitric oxide undergoes further reduction to nitrosothiol by further interaction with sulfhydryl groups.[18] Nitrosothiol activates guanylate cyclase in the vascular smooth muscle cells, thereby generating cyclic guanosine monophosphate (cGMP). It is this latter compound, cGMP, that produces smooth muscle relaxation by accelerating the release of calcium from these cells.[19,20]

Organic nitrate pharmacokinetics are quite complex because these agents are highly lipophilic and extensively distributed throughout the body.[21] Nitroglycerin is rapidly absorbed after buccal, sublingual, oral or topical administration. The onset, peak and duration of nitroglycerin action vary with the formulation: buccal and lingual aerosols and sublingual tablets have the most rapid onset of action and the shortest duration of action; oral sustained release and transdermal formulations have the slowest onset of action and the longest duration of action.

Nitroglycerin is extensively taken up and metabolized by the blood vessels themselves.[21] After oral administration, there is extensive first-pass metabolism in the liver. Nitroglycerin is also metabolized in circulating red blood cells.

Isosorbide dinitrate is less efficiently absorbed after sublingual, oral or topical administration compared with nitroglycerin and isosorbide mononitrate. The isosorbide compounds are less readily metabolized in the liver than is nitroglycerin. The more polar isosorbide mononitrate is *not* subject at all to hepatic first-pass metabolism.[21] Isosorbide mono- and dinitrate have fairly rapid onset of action and prolonged durations of action. The pharmacokinetics of isosorbide dinitrate are made more complicated by virtue of its partial metabolism to the active mononitrate. Finally, organic nitrate pharmacokinetics and pharmacodynamics are altered during sustained therapy, thereby further complicating these agents' pharmacologic actions. For example, isosorbide dinitrate blood levels are actually higher after several weeks of oral administration than after acute dosing. This observation suggests that isosorbide dinitrate clearance is reduced during chronic administration.[22] Nitrate metabolism and drug effect are not altered by food, smoking, renal or hepatic disease.[23] Most patients with congestive heart failure also respond to nitrate therapy.

Nitrate tolerance has been extensively examined and discussed elsewhere.[21,23,24] It is now widely accepted that at least partial vascular tolerance with attenuation of nitrate effect develops in many patients chronically treated with any nitrate compound. The mechanism of nitrate tolerance is poorly understood, but may relate to a deficiency of reduced sulfhydryl groups thereby leading to decreased production of nitrosothiols and cGMP.[15,23,24] The administration of N-acetylcysteine, a sulfhydryl group donor, decreases vascular tolerance to nitrates.[24,25] Longer intervals between nitrate doses, e.g., 8 to 10 hours can also decrease the development of tolerance.[24,26]

NITRATE THERAPY IN THE ELDERLY

As already discussed, elderly subjects often have a number of characteristics that make them prone to drug-induced untoward reactions (Tables I and II). A tendency to develop orthostatic hypotension and reduced baroreceptor function in the elderly can result in marked drug-related adverse reactions when vasodilators are used. Most clinicians are aware of this potential problem in elderly subjects and vasodilators such as organic nitrates are administered judiciously in order to prevent syncope or near-syncope.

There is a relative paucity of information concerning the pharmacokinetics and pharmacodynamics of nitrates in elderly subjects. In this regard, 2 experimental studies are of interest. Ioannides et al[27] examined volumes of distribution and elimination rates for nitroglycerin in a number of species. They sought species, gender and age differences in these variables. The plasma half-life of nitroglycerin was longer and the volume of distribution was larger in older animals. The larger volume of distribution led to lower plasma levels in older animals.[27] Clearance rates for nitroglycerin were not significantly altered by age. These investigators suggest that their observations are the result of declining hepatic microsomal enzyme levels in older animals leading to decreased metabolism of nitroglycerin in the liver. Moreover, older animals (and humans) have higher body fat contents. Nitroglycerin is highly lipophilic and this may also account, at least in part, for the observed prolongation of plasma half-life.[27]

Fleisch and Hooker[28] examined nitroglycerin-induced relaxation of vascular smooth muscle in rabbits and rats. Vascular smooth muscle relaxation after exposure to nitroglycerin was unaffected by age. Their observation that isoproterenol-induced smooth muscle relaxation declined with increasing age was of particular interest.[28] Because isoproterenol-induced smooth muscle relaxation is mediated via β_2-receptor stimulation, it is likely that this reduced responsiveness to isoproterenol is the result of declining receptor number or sensitivity with age. Since nitroglycerin-mediated smooth muscle relaxation is independent of β-adrenergic receptor function, it is not surprising that responses to nitroglycerin's actions are preserved in older animals.

Marchionni et al[29] examined the acute hemodynamic effects of intravenous nitroglycerin in 24 patients with acute myocardial infarction and left ventricular failure. They compared the responses in 2 groups of patients: persons aged $\geq$75 and those aged <65 years. They sought to reduce systemic arterial pressure by 5 to 10% during nitroglycerin infusion. This end point was achieved with significantly lower doses of nitroglycerin in the elderly patients. Moreover, the older patients had significantly

greater reductions in pulmonary arterial and pulmonary capillary wedge pressures compared with younger persons during nitroglycerin infusion.[29] The decline in systemic vascular resistance in response to nitroglycerin was similar in both groups of patients. The investigators concluded that elderly patients remain sensitive to the vascular smooth muscle actions of nitroglycerin. Since aging does not change the sensitivity of aortic smooth muscle to the actions of nitroglycerin,[28] it is likely that reduced metabolism of nitroglycerin in the liver[27] accounts for the lower effective dose in the elderly patient group. In addition, nitroglycerin reduced right atrial and pulmonary arterial pressures more in the elderly than in the young patients.[29] This difference in systemic venous response to nitroglycerin was believed by the investigators to be the result of either an age-dependent increased sensitivity of venous vascular smooth muscle or decreased circulating blood volume (Table I). Diminished blood volume has been previously cited as a reason for the hypotensive reactions that often occur in elderly subjects treated with vasodilating agents.[30]

Flaherty et al[31] administered intravenous nitroglycerin to 12 patients with acute myocardial infarction. Five of these patients were aged >65 years (mean 73.8), 5 other patients were aged <57 years (mean 50.8). A repeat analysis of their published data[31] demonstrates that the older patients had a mean decrease in left ventricular filling pressure of 11.0 mm Hg compared with 7.2 mm Hg in the younger subjects. Mean arterial blood pressure declined 6.4 mm Hg in the older subjects and 8.4 mm Hg in the younger patients. Mean cardiac index increased by 0.12 liters/min/m^2 in the younger patients and declined by 0.24 liters/min/m^2 in the older persons.[31] Taylor et al[32] studied 10 patients with chronic congestive heart failure (9 patients with ischemic heart disease and 1 patient with congestive cardiomyopathy) before and during the application of nitroglycerin ointment. Six of their patients were aged ≥65 years (mean 70.3), whereas 4 patients were aged <59 years (mean 55.8). A repeat analysis of their published data[32] also revealed that older subjects demonstrated a greater decrease in mean left ventricular filling pressures than did younger persons (10.2 vs 8.0 mm Hg). Decreases in mean arterial blood pressure and increases in mean cardiac index were virtually identical in both patient groups (blood pressure decreases in older vs younger persons, 5.5 vs 5.3 mm Hg; cardiac index increases in older vs younger persons, 0.41 vs 0.43 liters/min/m^2).

Taken together, these latter 2 studies[31,32] support the observations of Marchionni et al.[29] Elderly subjects remain sensitive to the vascular smooth muscle actions of organic nitrates. It appears that the venous smooth muscle action of nitroglycerin is increased in older patients, probably as a result of decreased nitrate metabolism.

Elderly patients are often mouth breathers; they may manifest decreased saliva production. Taken together, these 2 factors may delay the dissolution of sublingually administered nitrate formulations. Reisen et al[33] demonstrated that isosorbide dinitrate spray relieved exercise-induced angina pectoris more rapidly than sublingual tablets in 9 elderly patients (mean age 67 years) with coronary artery disease. This investigation underscores the fact that subtle differences in bioavailability of nitrate formulations may exist between younger and older patients.

There are no studies that specifically compare nitrate pharmacokinetics and pharmacodynamics in younger compared with older persons. However, Armstrong et al[34] reported nitroglycerin clearance rates in 16 patients with congestive heart failure given varying doses of intravenous nitroglycerin. Within these reported data were 4 patients >65 years (mean age 66.5) and 6 patients <55 years (mean 47.8). A repeat analysis of their published data[34] revealed no difference in nitroglycerin clearance rates between older and younger patients (mean total body clearance in older vs younger patients, 10.7 vs 10.5 liters/min). Despite this lack of difference in nitroglycerin clearance rates between older and younger subjects, Come and Pitt[35] noted that nitroglycerin-induced severe hypotension and bradycardia were more common in elderly patients with myocardial infarction than in younger persons. Three of their 5 reported cases were patients aged >65 years (67, 77 and 78 years). Thus, the limited hemodynamic and pharmacokinetic data available all point in the same direction as the clinical observations. Elderly subjects apparently demonstrate increased vascular (especially venous) smooth muscle action from organic nitrates. Accordingly, clinicians should use smaller initial doses of organic nitrates in elderly subjects. Nitrate dosage can be progressively increased once the sensitivity of the individual patient to nitrates has been observed.

In conclusion, it is apparent that elderly patients can benefit from organic nitrate therapy. However, it is important for the clinician to remember the changes that occur in the cardiovascular system with aging. These alterations sensitize the elderly subject to the vascular smooth muscle actions of nitrates. Initial dosages of nitrates should be less than in younger patients.

Recently, Marchionni et al[36] demonstrated that the increased sensitivity of elderly patients to nitroglycerin is the result of pharmacodynamic changes in these patients, i.e., dampened baroreceptor responsivity to nitroglycerin-induced hypotension.

REFERENCES

1. Balcon R. Pacing. In: Hamer J, ed. Recent Advances in Cardiology. *Edinburgh: Churchill Livingstone, 1973:217–230.*

2. Hickler RB, Li L, Alpert JS. Contribution of cardiac and vascular factors to systolic hypertension in the elderly. *Geriatric Cardiovasc Med 1988;1:53–60.*

3. Safar ME, Toto-Moukono JJ, Bouthier JA, Asmar RE, Levenson JA, Simon AC, London GM. Arterial dynamics, cardiac hypertrophy, and antihypertensive treatment. *Circulation 1987;75:suppl I:I-156–I-161.*

4. Lakatta EG, Mitchell JH, Pomerance A, Rowe GG. Human aging: Changes in structure and function. *J Am Coll Cardiol 1987;10:(suppl A):42A–47A.*

5. Rowe JW. Clinical consequences of age-related impairments in vascular compliance. *Am J Cardiol 1987;60:68G–71G.*

6. Gribbon G, Pickering TG, Slight P, Peto R. Effect of age and high blood pressure on baroreflex sensitivity in man. *Circ Res 1971;29:424–427.*

7. Collins KJ. Functional changes in autonomic nervous responses with aging. *Age Ageing 1980;9:17–20.*

8. Amorim DS, Neto JAM, Maciel BC, Gallo L, Fiho JT, Manco JC. Cardiac autonomic function in healthy elderly people. *Geriatric Cardioasc Med 1988;1:65–71.*

9. Lamy PP. Prescribing for the Elderly. Littleton, MA: PSG Publishing, 1980.

10. McAllister RG Jr. Age-related changes in drug handling in man. *Am J*

Cardiol 1986;57:59C–62C.
11. Miller RR, Greenblat DJ, eds. Drug Effects in Hospitalized Patients. Experiences of the Boston Collaborative Drug Surveillance Program 1966–1975. *New York: John Wiley, 1976.*
12. Imhof PR, Sieber A, Hodler J, Muller P, Ott B, Fankhauser P, Chu LC, Gerardin A. Plasma concentrations and haemodynamic effects of nitroglycerin during and after intravenous infusion in healthy volunteers. *Eur J Clin Pharmacol 1982;23:99–106.*
13. Feldman RL, Pepine CJ, Conti CR. Magnitude of dilation of large and small coronary arteries by nitroglycerin. *Circulation 1981;64:324–333.*
14. Brown BG, Bolson E, Petersen RB, Pierce CD, Dodge HT. The mechanisms of nitroglycerin action: stenosis vasodilation as a major component of drug response. *Circulation 1981;64:1089–1097.*
15. Ignarro LJ, Lippton H, Edwards JC, Baricos WH, Hyman AL, Kadowitz PJ, Gruetter CA. Mechanism of vascular smooth muscle relaxation by organic nitrates, nitrites, nitroprusside and nitric oxide: evidence for the involvement of S-nitrosothiols as active intermediates. *J Pharmacol Exp Ther 1981;218:739–749.*
16. Kobayashi A, Suzuki Y, Kamikawa T, Hayashi H, Yamazaki N. The effects of nitroglycerin on cyclic nucleotides in the coronary artery in vivo. *Life Sci 1980;27:1679–1685.*
17. Winniford MD, Kennedy PL, Wells PJ, Hillis LD. Potentiation of nitroglycerin-induced coronary dilation by N-acetylcysteine. *Circulation 1986;73:138–142.*
18. Ignarro LJ, Gruetter CA. Requirement of thiols for activation of coronary arterial guanylate cyclase by glyceryl trinitrate and sodium nitrite: Possible involvement of S-nitrosothiols. *Biochim Biophys Acta 1980;631:221–231.*
19. Popescu LM, Panouiu C, Hinescu M, Nuto O. The mechanism of cGMP-induced relaxation in vascular smooth muscle. *Eur J Pharmacol 1985;107:393–394.*
20. Murad F. Cyclic guanosine monophosphate as a mediator of vasodilation. *J Clin Invest 1986;78:1–5.*
21. Fung HL. Pharmacokinetics and pharmacodynamics of organic nitrates. *Am J Cardiol 1987;60:4H–9H.*
22. Thadani U, Fung H, Darke AC, Parker JO. Oral isosorbide dinitrate in angina pectoris. Comparison of duration of action and dose response relationship during acute and sustained therapy. *Am J Cardiol 1982;49:411–417.*
23. Abrams J. Pharmacology of nitroglycerin and long-acting nitrates. *Am J Cardiol 1985;56:(suppl A):12A–18A.*
24. Parker JO. Nitrate therapy in stable angina pectoris. *N Engl J Med 1987;316:1635–1642.*
25. Torresi J, Horowitz JD, Dusting GJ. Prevention and reversal of tolerance to nitroglycerin with N-acetylcysteine. *J Cardiovasc Pharmacol 1985;7:777–783.*
26. Flaherty JT. Hemodynamic attenuation and the nitrate-free interval: alternative dosing strategies for transdermal nitroglycerin. *Am J Cardiol 1985;56:321–371.*
27. Ioannides C, Parke DV, Taylor IW. Elimination of glyceryl trinitrate: effects of sex, age, species, and route of administration. *Br J Pharmacol 1982;77:83–88.*
28. Fleisch JH, Hooker CS. The relationship between age and relaxation of vascular smooth muscle in the rabbit and rat. *Circ Res 1976;38:243–249.*
29. Marchionni N, Schneeweiss A, DiBari M, Ferrucci L, Moschi G, Salani B, Paoletti M, Burgisser C, Fumagalli S. Age-related hemodynamic effects of intravenous nitroglycerin for acute myocardial infarction and left ventricular failure. *Am J Cardiol 1988;61:81E–83E.*
30. Chobanian AV. Pathophysiologic considerations in the treatment of the elderly hypertensive patient. *Am J Cardiol 1983;52:49D–53D.*
31. Flaherty JT, Reid PR, Kelly DT, Taylor DR, Weisfeldt ML, Pitt B. Intravenous nitroglycerin in acute myocardial infarction. *Circulation 1975;51:132–139.*
32. Taylor WR, Forrester JS, Magnusson P, Takano T, Chatterjee K, Swan HJC. Hemodynamic effects of nitroglycerin ointment in congestive heart failure. *Am J Cardiol 1976;38:469–473.*
33. Reisen LH, Landau E, Darawski A. More rapid relief of pain with isosorbide dinitrate oral spray than with sublingual tablets in elderly patients with angina pectoris. *Am J Cardiol 1988;61:2E–3E.*
34. Armstrong PW, Armstrong JA, Marks GS. Pharmacokinetic-hemodynamic studies of intravenous nitroglycerin in congestive heart failure. *Circulation 1980;62:160–166.*
35. Come PC, Pitt B. Nitroglycerin-induced severe hypotension and bradycardia in patients with acute myocardial infarction. *Circulation 1976;54:624–628.*
36. Marchionni N, Ferrucci L, Boncinelli L, Salani B, DiBari M, Moschi G, Paoletti M, Burgisser C. Age-related changes in the pharmacodynamics of intravenous glyceryl trinitrate. *Aging 1990;in press.*

Nitrate Tolerance in Heart Failure: Differential Venous, Pulmonary and Systemic Arterial Effects

Nabeel Makhoul, MD, Nader Dakak, MD, Moshe Y. Flugelman, MD, Amnon Merdler, MD, Arie Shefer, MD, Adam Schneeweiss, MD, David A. Halon, MB, ChB, and Basil S. Lewis, MD

The hemodynamic profile of tolerance to intravenous nitroglycerin was studied in 9 patients with New York Heart Association Class III to IV congestive heart failure. After rapid dosage build-up to the maximal tolerated dose (decrease in pulmonary wedge pressure to 10 mm Hg or systolic blood pressure to 90 mm Hg), nitroglycerin (525 ± 548 μg/min) was administered at a constant continuous intravenous infusion for a total of 24 hours. The extent of nitrate tolerance at 24 hours was calculated as the percentage loss of the benefit achieved at time of peak effect of nitroglycerin. Tolerance had a different time course and magnitude in the venous, arterial and pulmonary circulations. At 24 hours, right atrial pressure and pulmonary vascular resistance returned to control values in most patients, while 40 to 50% of the effect on systemic vascular resistance, cardiac index and pulmonary wedge pressure was maintained. These findings emphasize the importance of precise definitions in studies relating to nitrate tolerance.

(Am J Cardiol 1990;65:28J–31J)

From the Department of Cardiology, Lady Davis Carmel Hospital, Haifa, Israel.

Address for reprints: Basil S. Lewis, MD, Department of Cardiology, Lady Davis Carmel Hospital, 7 Michal Street, Haifa, 34362 Israel.

The development of nitrate tolerance may negate the beneficial effect of nitrate therapy in the management of patients with congestive heart failure.[1–7] At constant doses of nitrates,[7] ventricular filling pressures and cardiac output return toward baseline values in many patients within 24 to 48 hours. Development of nitrate tolerance is not always predictable[8] from baseline parameters.

Published reports on the definition and prevalence of nitrate tolerance is somewhat unclear; there is no consensus regarding its manifestations in different parts of the circulation.[9,10] The present study was undertaken to characterize in more detail the magnitude, hemodynamic spectrum and temporal course of tolerance developing during intravenous nitroglycerin therapy. The extent of tolerance was quantitated separately for the systemic, pulmonary and venous circulations, an approach that may provide a framework for further studies of tolerance and its mechanisms.

METHODS

Patients: The study consisted of 9 patients (8 men and 1 woman, aged 38 to 78 years) with severe (New York Heart Association class III to IV) heart failure with sinus rhythm, who required hemodynamic monitoring as part of their clinical management. The cause of heart failure in all patients was advanced coronary artery disease with extensive fixed regional and global left ventricular dysfunction. Long-acting nitrate therapy was discontinued at least 48 hours before the study, as was all other vasodilator therapy. Baseline drug therapy with digoxin (4 patients) and furosemide (8 patients; dose 40 to 80 mg/day) was continued at a constant dosage schedule throughout the study period. Diuretic drugs, when administered, were given at the same time each day, 6 hours after commencement and stabilization of the nitrate dosage.

Data acquisition: A flow-directed catheter was positioned in the pulmonary artery and an arterial line in the radial artery 12 to 18 hours before measurements were obtained.

Pressures were measured in the right atrium, pulmonary artery and pulmonary capillary wedge position, as well as from the radical arterial line. In the absence of mitral stenosis, the pulmonary capillary wedge pressure (PCWP) represents left ventricular end-diastolic pressure. Patients included in the study had a wedge pressure of ≥16 mm Hg and systolic blood pressure ≥90 mm Hg.

Cardiac output and stroke volume were measured by thermodilution in triplicate at each stage of the study protocol. When a measurement deviated by more than

TABLE I Effect of Intravenous Nitroglycerin (NTG) on Hemodynamic Measurements

	Effect of NTG (% Change at Peak Effect)				
Case	RAP	PVR	PCW	CI	SVR
1	−100	−52	−80	39	−32
2	−95	−73	−70	50	−24
3	−83	—	−45	0	−22
4	−54	−41	−32	57	−45
5	−73	−38	−44	19	−21
6	−100	−58	−56	0	−24
7	—	−49	−43	68	—
8	−38	−71	−53	55	−47
9	−100	−7	−62	19	−52
Mean ± SD	−80 ± 24	−49 ± 21	−54 ± 15	34 ± 25	−30 ± 11

CI = cardiac index; PCW = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SD = standard deviation; SVR = systemic vascular resistance.

TABLE II Tolerance to Continuous Intravenous Nitroglycerin (NTG) at 24 hours

	Loss of Effect of NTG (% Tolerance)				
Case	RAP	PVR	PCW	CI	SVR
1	266	189	115	55	79
2	19	19	52	54	49
3	14	—	11	—	30
4	85	0	44	0	0
5	125	194	25	80	65
6	200	97	77	—	130
7	—	113	83	54	—
8	66	13	72	45	44
9	100	80	50	40	44
Mean ± SD	125 ± 78	88 ± 76	59 ± 31	47 ± 24	55 ± 38

Abbreviations as in Table I.

10% from the other 2 values, this value was discarded and an additional determination made. Cardiac index was the cardiac output normalized for body surface area.

Administration of nitroglycerin: After hemodynamic measurements were obtained in the control state, nitroglycerin was administered by continuous intravenous infusion, increasing the dose rapidly over a period of 60 to 90 minutes until (1) the PCWP decreased to ≤10 mm Hg, or (2) systolic blood pressure decreased to ≤90 mm Hg. This dose (60 to 1,600 μg/min, mean 525 ± 548) was then continued unchanged throughout the study period. Hemodynamic measurements were repeated 3, 6, 12 and 24 hours after the onset of infusion of nitroglycerin.

Quantitation of nitrate tolerance: The extent of nitrate tolerance was calculated separately for each hemodynamic parameter, as the percentage loss of the maximal effect achieved by nitroglycerin, e.g., for the extent of tolerance with regard to right atrial (RA) pressure, tolerance (%) = (measured RA pressure − minimal RA pressure) × 100/(control RA pressure − minimal RA pressure). For each hemodynamic parameter, the time at which the maximal change occurred after the onset of nitroglycerin infusion was noted.

Statistical analysis: The effect of nitroglycerin at the time of each measurement was assessed by comparison with the data before administration of nitroglycerin using

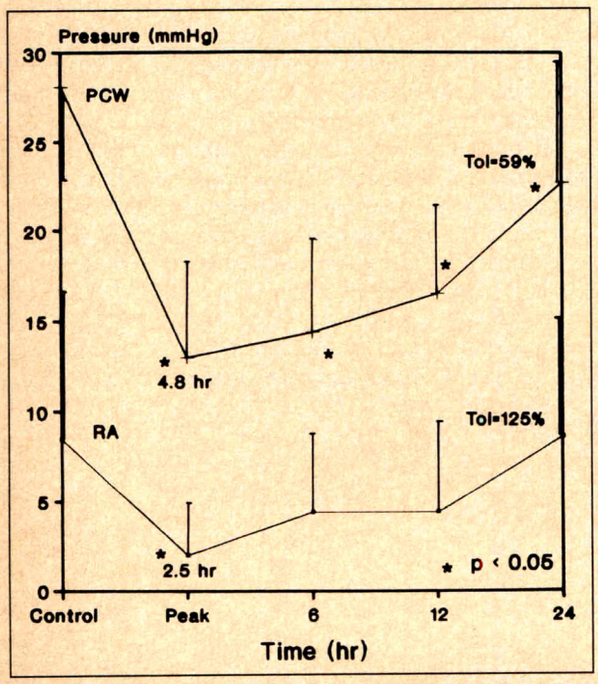


FIGURE 1. Right atrial (RA) and pulmonary capillary wedge (PCW) pressures (mean ± standard deviation) in the control state and during intravenous infusion of nitroglycerin. The maximal (peak) effect and the time of its occurrence is shown. Nitroglycerin reduced both RA and PCW pressure (p values compare each curve with the respective control value). At 24 hours 125% of the effect of nitroglycerin on RA, but only 59% of the effect on PCW, was lost. Tol = tolerance.

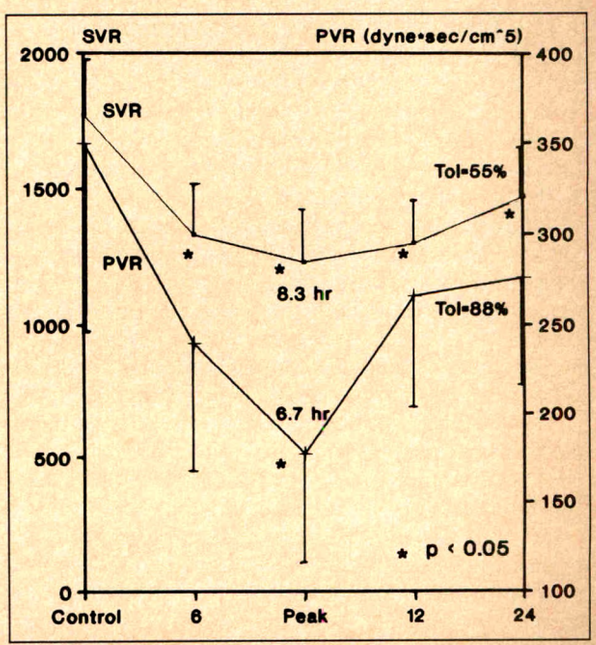


FIGURE 2. Systemic (SVR) and pulmonary (PVR) vascular resistance during nitroglycerin infusion. The maximal (peak) effect occurred later for SVR and tolerance (Tol) was less marked.

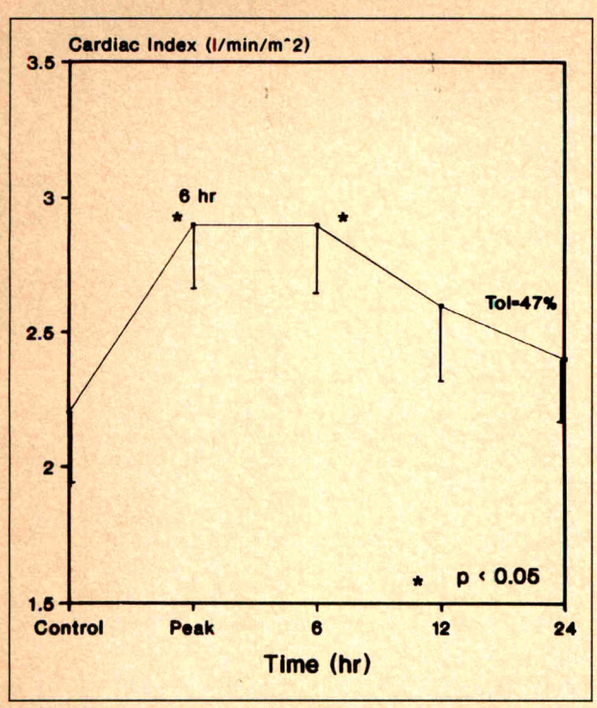


FIGURE 3. Cardiac index before and during nitroglycerin infusion. The peak effect occurred at 6 hours. Half the effect was lost at 24 hours. Tol = tolerance.

Student *t* test for paired data, with correction for multiple comparisons.

RESULTS

Effect of intravenous nitroglycerin: Nitroglycerin reduced RA pressure from 9 ± 7 to a nadir of 2 ± 2 mm Hg ($p < 0.05$), PCWP from 28 ± 4 to 13 ± 4 mm Hg ($p < 0.001$), pulmonary vascular resistance from 355 ± 217 to 177 ± 124 dynes·s·cm^{-5} ($p < 0.02$) and systemic vascular resistance from 1,774 ± 417 to 1,235 ± 348 dynes·s·cm^{-5} ($p < 0.001$). Cardiac index increased from 2.2 ± 0.5 to 2.9 ± 0.5 liters/min/m^2 ($p < 0.01$). Heart rate was unchanged (82 ± 18 vs 84 ± 19 beats/min, difference not significant [NS]).

The percentage change was greater for the right-sided measurements (RA vs PCWP, $p = 0.02$; pulmonary vs systemic vascular resistance, $p = 0.04$) (Table I). There was no relation between the percentage change in pulmonary vascular resistance and the change in RA pressure, nor was there a significant relation between the change in systemic vascular resistance and the change in PCWP.

Time course of effect of nitroglycerin on hemodynamic measurements: The peak effect of nitroglycerin on RA pressure was observed after 2.5 ± 3.9 hours, depending essentially on the rate of increase of nitroglycerin dosage. The peak effect on PCWP was reached after 4.8 ± 3.5 hours, on cardiac index after 6.0 ± 7.7 hours, on pulmonary vascular resistance after 6.7 ± 8.0 hours and on systemic vascular resistance after 8.3 ± 7.6 hours ($p = 0.07$ compared with time to peak effect for RA pressure).

Nitrate tolerance: Attenuation of the effect of nitroglycerin occurred between 12 and 24 hours after the commencement of the nitroglycerin infusion. There was marked individual variability in the extent of attenuation at 24 hours (Table II), and also in the degree of attenuation for different hemodynamic measurements, particularly with a greater degree of tolerance for right-sided measurements. At 24 hours, RA pressure returned to baseline (125 ± 78% tolerance), whereas for PCWP only 59 ± 31% of the effect was lost (RA vs wedge tolerance, $p = 0.05$) (Fig. 1). Similarly, 88 ± 76% of the effect on pulmonary vascular resistance was lost at 24 hours, whereas tolerance for systemic resistance was less (55 ± 38%) (pulmonary vs systemic tolerance, $p = NS$) (Fig. 2). A moderate degree of tolerance (47 ± 24%) was observed for cardiac index (Fig. 3), similar to that for other left-sided measurements.

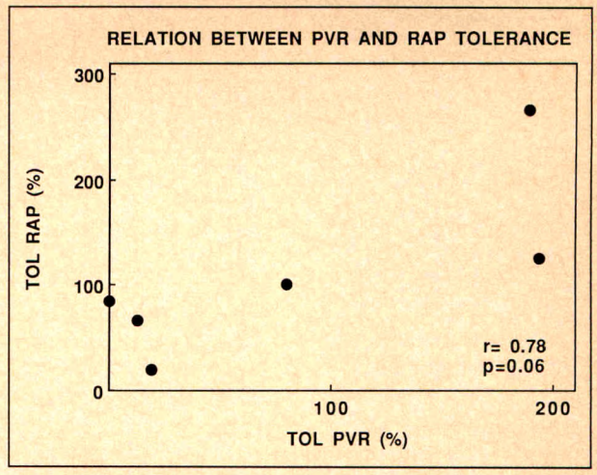


FIGURE 4. Linear relation between percentage tolerance (TOL) developing for pulmonary vascular resistant (PVR) and that for right atrial pressure (RAP).

RA tolerance was directly related to the degree of tolerance for pulmonary vascular resistance ($r = 0.78$, $p < 0.05$) (Fig. 4). The degree of tolerance for the effect of nitrates on PCWP was related to the percentage tolerance observed with regard to systemic vascular resistance ($r = 0.51$, NS) (Fig. 5).

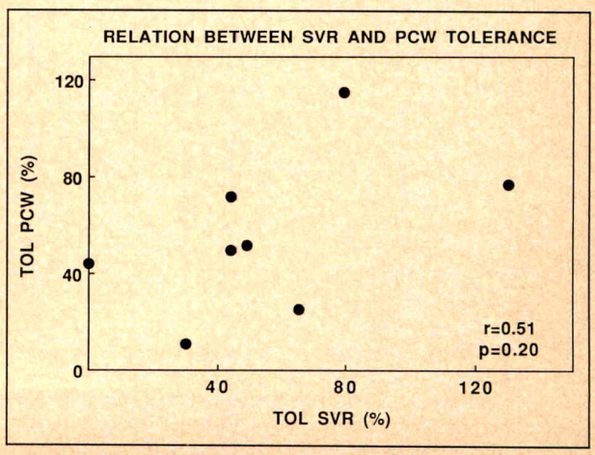


FIGURE 5. Relation between percentage tolerance (TOL) for pulmonary capillary wedge (PCW) pressure and that for systemic vascular resistance (SVR).

DISCUSSION

Hemodynamic effects of nitroglycerin: The hemodynamic effects of nitroglycerin differed markedly in different parts of the circulation. Both RA pressure and pulmonary vascular resistance decreased rapidly. However, there was a considerably greater and more rapid effect of nitrates on RA pressure, probably reflecting a greater affinity or effect of the drug on the systemic venous system rather than the pulmonary arterial circulation.[11–13] Because nitrates were administered by intravenous infusion, the concentration and effect of nitrates would be expected to be greatest in the pulmonary arterial circulation and lowest in the systemic venous system. Cossum et al[14] showed that nitrate infusion into the right femoral vein in sheep produced the highest concentration of nitrates in the pulmonary arterial system, the next highest concentration in the left ventricle and systemic arterial circulation, followed by lower levels of nitrates in the systemic veins. Differential blood levels, related to the site of infusion of nitroglycerin, may also explain the less prominent and much later effect of nitrates on the systemic vascular resistance and on left ventricular filling pressure (PCWP) in this and most published studies.

Nitrate tolerance and its mechanisms: Tolerance to nitroglycerin occurred in most patients in the study. The extent of tolerance and its manifestations showed considerable individual variability. The greatest degree of tolerance was observed for RA pressure, with a loss of most or all efficacy of the drug at 24 hours in 6 of 8 patients. In contrast, at the same point in time, approximately half the benefit gained by nitrates was still present with respect to left heart hemodynamics and cardiac index. For both right- and left-sided cardiac filling pressures, the degree of tolerance was directly related to the loss of effect of nitrates on the corresponding vascular resistance, probably reflecting a secondary increase in the impedance to cardiac emptying. Individual differences in the extent of nitrate tolerance may be related to the severity of heart failure, degree of edema[15,16] or initial systemic vascular resistance.[8]

The precise mechanisms underlying the development of nitrate tolerance are related to (1) a cellular mechanism, in which high concentrations of nitrates exhaust the cellular content of sulfhydryl groups and result in the capability of the cell to convert nitrates to S-nitrosothiols,[17–20] and (2) a systemic mechanism, in which rapid and marked decreases in intravascular pressures may trigger an enhanced neurohumoral response, increased secretion of renin and aldosterone, with secondary fluid retention as the cause of the return of left- and right-sided cardiac filling pressures toward baseline or higher values.[5,21,22] This study is in keeping with the biochemical concept relating to the development of tolerance. A high concentration and affinity of nitrates for the systemic venous and pulmonary arterial circulations would more rapidly exhaust the nitrate biochemical pathway in these vascular beds, and explain the greater degree of nitrate tolerance in these parts of the circulation.

Moreover, because right heart chambers adapt more easily to volume load, fluid retention as the mechanism of tolerance would be expected to produce a lesser effect on RA than on PCWP.

Implications: The individual variation in the magnitude and time course of nitrate tolerance and its variability in different parts of the circulation emphasize the fact that studies relating to nitrate tolerance should be evaluated in terms of the precise definition of tolerance used by the investigators. In clinical patient management, the dose and route of nitrate administration should be tailored according to the individual response of the patient.

REFERENCES

1. Abrams J. Tolerance to organic nitrates. *Circulation 1986;74:1181–1185.*

2. Sharpe D, Coxon R. Nitroglycerin in transdermal therapeutic systems in chronic heart failure. *J Cardiovasc Pharmacol 1984;6:76–82.*

3. Jordan RA, Seth L, Henry DA, Wilen MM, Franciosa JA. Dose requirements and hemodynamic effects of transdermal nitroglycerin compared with placebo in patients with congestive heart failure. *Circulation 1985;71:980–986.*

4. Jordan RA, Seth L, Caseblot P, Hayes MJ, Wilen MM, Franciosa J. Rapidly developing tolerance to transdermal nitroglycerin in congestive heart failure. *Ann Intern Med 1986;104:295–298.*

5. Packer M, Medina N, Yushak N, Lee WH. Hemodynamic factors limiting the response to transdermal nitroglycerin in severe congestive heart failure. *Am J Cardiol 1986;57:260–267.*

6. Roth A, Kulick D, Freidenberger L, Hong R, Rahimtoola SH, Elkayam U. Early tolerance to hemodynamic effects of high dose transdermal nitroglycerin in responders with severe congestive heart failure. *J Am Coll Cardiol 1987;9:858–864.*

7. Packer M, Lee WH, Kessler PD, Gottlieb S, Medina N, Yushak M. Prevention and reversal of nitrate tolerance in patients with congestive heart failure. *N Engl J Med 1987;317:799–804.*

8. Elkayam U, Kulick D, McIntosh N, Roth A, Hsueh W, Rahimtoola SH. Incidence of early tolerance to hemodynamic effects of continuous infusion of nitroglycerin in patients with coronary artery disease and heart failure. *Circulation 1987;3:577–584.*

9. Leier CV, Huss P, Magorien RD, Unverferth DV. Improved exercise capacity and differing arterial and venous tolerance during chronic isosorbide dinitrate therapy for congestive heart failure. *Circulation 1983;67:817–822.*

10. Stewart DJ, Elsner D, Sommer D, Holtz J, Bassenge E. Altered spectrum of nitroglycerin action in long-term treatment: nitroglycerin—specific venous tolerance with maintenance of arterial vasodepressor potency. *Circulation 1986;74:573–582.*

11. Abrams J. Hemodynamic effects of nitroglycerin and long acting nitrates. *Am Heart J 1985;110:216–224.*

12. Imhof PR, Ott B, Frankhauser P, Chu LC, Holder J. Difference in nitroglycerin dose response in the venous and arterial beds. *Eur J Clin Pharmacol 1980;18:455–460.*

13. Leier CV, Bambash D, Thompson MJ, Cattaneo SM, Goldberg RJ, Unverferth DV. Central and regional hemodynamic effects of intravenous isosorbide dinitrate, nitroglycerin and nitroprusside in patients with congestive heart failure. *Am J Cardiol 1981;48:1115–1123.*

14. Cossum PA, Roberts MS, Yong AC, Kilpatrick D. Distribution and metabolism of nitroglycerin and its metabolites in vascular beds of sheep. *J Pharmacol Exp Ther 1986;237:959–966.*

15. Magrini F, Niarchos A. Ineffectiveness of sublingual nitroglycerin in acute left ventricular failure in the presence of massive peripheral edema. *Am J Cardiol 1980;45:841–847.*

16. Magrini F, Niarchos A. Hemodynamic effects of massive peripheral edema. *Am Heart J 1983;105:90–97.*

17. Needleman P, Johnson EM. Mechanism of tolerance development to organic nitrates. *J Pharmacol Exp Ther 1973;184:709–715.*

18. Ignarro LJ, Lippton H, Edwards JC, Baricos WH, Hyman A, Kadowitz PJ, Gruetter CA. Mechanism of vascular smooth muscle relaxation by organic nitrates, nitrites, nitroprusside and nitric oxide: evidence for the involvement of S-nitrosothiols as active intermediates. *J Pharmacol Exp Ther 1981;218:739–749.*

19. Yeates RA, Laufen H, Leitold M. The reaction between organic nitrates and sulfhydryl compounds: a possible model system for the activation of organic nitrates. *Mol Pharmacol 1985;28:555–559.*

20. Ahlner J, Axelsson KL. Nitrates: mode of action at a cellular level. *Drugs 1987;33:suppl 4:32–38.*

21. Packer M, Meller J, Medina N, Yushak M, Corlin R. Determinants of drug response in severe chronic heart failure. I. Activation of vasoconstrictor forces during vasodilator therapy. *Circulation 1981;64:506–514.*

22. Lis Y, Bennett D, Lambert G, Robson D. A preliminary double blind study of intravenous nitroglycerin in acute myocardial infarction. *Intensive Care Med 1984;10:179–184.*

Efficacy of Isosorbide-5-Mononitrate on Painful and Silent Myocardial Ischemia After Myocardial Infarction

Jianzhang Feng, MD, Xiu-Hua Feng, MD, and Adam Schneeweiss, MD

The anti-ischemic efficacy of isosorbide-5-mononitrate, 20 mg 3 times daily, on silent myocardial ischemia after myocardial infarction was studied in 28 Chinese patients with use of 48 hours of ambulatory electrocardiographic monitoring in a randomized, crossover, single-blind, placebo-controlled study. Isosorbide mononitrate reduced both painful and painless episodes of ischemia compared with placebo. The number of total ischemic episodes was reduced 88%, duration of ischemia 94%, time-ischemia integral 95%, and total maximal ST-segment depression 86% ($p < 0.01$). The drug did not alter the heart rate and blood pressure, and had no evident adverse effect. Thus, isosorbide mononitrate is effective and well tolerated in postinfarction patients with silent ischemia.

(Am J Cardiol 1990;65:32J–35J)

From Guangdong Provincial Cardiovascular Institute, Guangzhou, People's Republic of China and the Cardiovascular Research Foundation, Geneva, Switzerland.

Address for reprints: Adam Schneeweiss, MD, Sauerberg 12, D-6208 Bad Schwalbach 7, Federal Republic of Germany.

It was shown that silent myocardial ischemia may be related to myocardial infarction, reinfarction, severe arrhythmia or cardiomyopathy.[1] Its prognostic and therapeutic significance in coronary artery disease has not been clearly established, although it has been shown that silent ischemia is an independent predictor of poor prognosis.[2] The need for and type of treatment of silent ischemia are still controversial.[3] However, if the silent ST-segment depression is accepted as ischemia, it is logical to treat it. Almost all therapeutic research until now has been concentrated on Caucasian patients. Since 1987, we used isosorbide-5-mononitrate (IS-5-MN) (Elantan®) to treat silent myocardial ischemia in Chinese patients with coronary artery disease. This study reports on the effect of IS-5-MN on silent myocardial ischemia in patients with coronary artery disease evaluated by 48-hour ambulatory electrocardiographic monitoring in a randomized, crossover, single-blind, placebo-controlled study.

METHODS

Patients: Twenty-eight patients were enrolled in the study (26 men and 2 women, aged 42 to 78 years [mean 60]). All patients had a definitive history of acute myocardial infarction. Among them, 12 patients had anterior wall infarction, 9 patients inferior wall infarction, 2 patients subendocardial infarction and 5 patients had anterior and inferior infarction. Of these, 8 patients had no angina pectoris after the infarction, 18 patients had mild angina and 2 patients had moderate angina. No patient had bundle branch block or another organic heart disease.

Medication: The medications included isosorbide-5-mononitrate, 20-mg tablets, and matching placebo. The dosage was 20 mg 3 times daily. The medications were given in a double-blind design.

Protocol: All patients stopped taking any antianginal drugs 3 days before entering the study. On the fourth day, the patients underwent physical examination and 48 hours of ambulatory electrocardiographic monitoring as the baseline control. Then they were randomized into 2 groups: group A patients received placebo for 2 weeks and group B patients received IS-5-MN for 4 weeks. Thereafter the treatment groups were crossed over. At the end of each phase, ambulatory electrocardiographic monitoring was performed for 48 hours. During the entire study period, heart rate and blood pressure were measured each week, the number of anginal attacks and the

TABLE I Change in Total Myocardial Ischemia (Painful + Painless) After Medication in 28 Patients per Week

	Baseline Phase (1)	Placebo Phase (2)	Elantan Phase (3)	Decreased (%)
No. of ischemic episodes	532	546	66	88
Duration of ischemia (min)	10,203	10,613	654	94
Integration (mm/min)	21,748	22,407	1,039	95
Total maximal ST segment (min)	1,012	1,055	142	86

* p value: phase 1 and 2: >0.05; phase 1 and 3 and 2 and 3: <0.01.

TABLE II Change in Silent Myocardial Ischemia After Medication in 28 Patients per Week

	Baseline Phase (1)	Placebo Phase (2)	Elantan Phase (3)	Decreased (%)
No. of ischemic episodes	522	538	64	88
Duration of ischemia (min)	10,121	10,237	622	94
Integration (mm/min)	21,391	21,792	925	96
Total maximal ST segment (min)	1,001	1,037	142	86

* p value: phase 1 and 2: >0.05; phase 1 and 3 and 2 and 3: <0.01.

adverse effects were recorded. Sublingual nitroglycerin tablets were allowed for treatment of episodes of angina pectoris.

Ambulatory electrocardiographic monitoring: Ambulatory electrocardiographic monitoring for 48 hours was performed. Holter equipment manufactured by Marquette Electronics Company was used. The frequency response of the recorder was 0.05 to 100 Hz. All the tapes of record were analyzed by a Marquette 8000 laser Holter analysis system which can automatically analyze the number of ischemic episodes, duration of ischemia, integration and total maximal ST-segment of ischemia.

The criteria of myocardial ischemia were horizontal or downsloping ST-segment depression ≥0.1 mV persisting for ≥1 minute. The interval required to differentiate between 2 episodes was ≥1 minute. If the ischemia was not accompanied by symptoms, it was defined as silent myocardial ischemia.[4]

Data analysis: To evaluate the effect of medications on ischemia the following parameters were measured: (1) number of ischemic episodes, (2) duration of ischemia in minutes (the sum of durations of each myocardial ischemic episode), (3) integration of ST deviation time (ST-segment depression multipled by its duration in minutes [mm/min]), and (4) total maximal ST depression (the sum of severity of each episode of myocardial ischemia).

The observation period was divided into 3 phases: (1) baseline phase—patients did not receive anti-ischemic drugs for 3 days; (2) placebo period—patients took placebo for 2 weeks; and (3) IS-5-MN period—patients took IS-5-MN for 4 weeks.

RESULTS

Effect on myocardial ischemia: The change of total ischemia (painful/painless) in number, duration, integration and total maximal ST depression of ischemia in the 3-phase stage is summarized in Table I.

When the placebo phase was compared with the IS-5-MN phase, the total ischemia (painful + painless) in

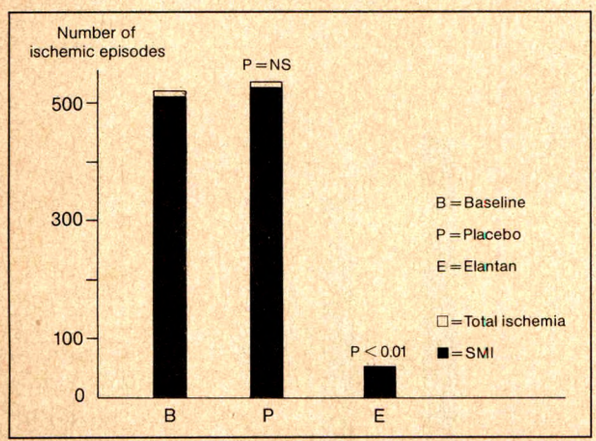


FIGURE 1. Number of ischemic episodes before and after treatment. NS = not significant.

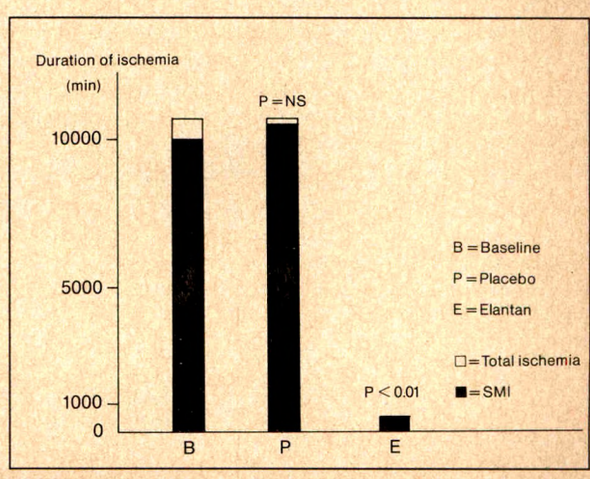


FIGURE 2. Duration of ischemia before and after treatment. NS = not significant.

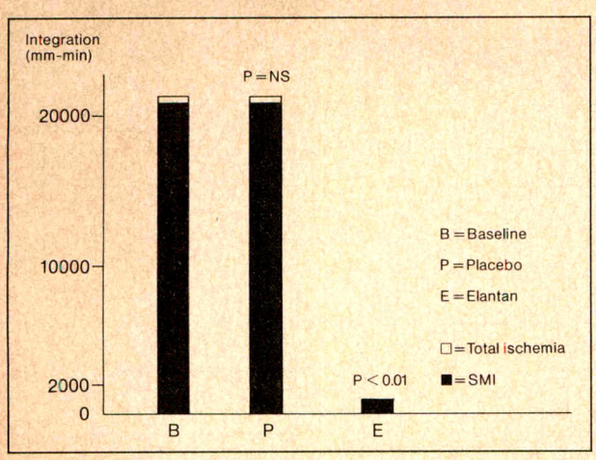


FIGURE 3. Integral of ischemia—duration before and after treatment. NS = not significant.

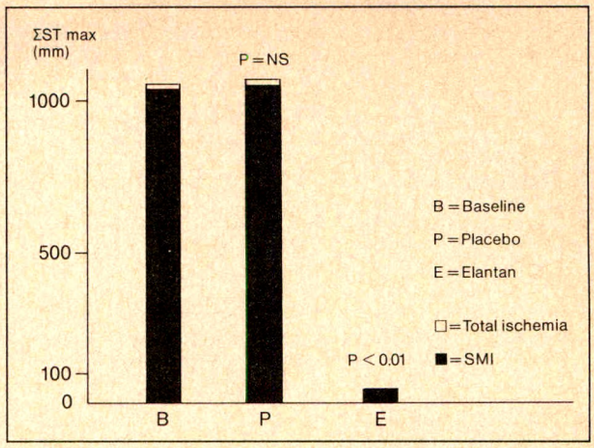


FIGURE 4. Integral of total maximal ST depression (Σ ST max) before and after treatment. NS = not significant.

number, duration, integration and total maximal ST depression was decreased 88, 94, 95 and 86%, respectively. The number, duration, integration and total maximal ST depression of silent myocardial ischemia were decreased by 88, 94, 96 and 86%, respectively (Table II) (Fig. 1 to 4).

Comparison between the daily spontaneous variability of ischemia and the effect of isosorbide-5-mononitrate on ischemia: To differentiate the effect of daily spontaneous variability from that of medication, we compared the change of silent myocardial ischemia in number, duration, integration and total maximal ST depression between the daily spontaneous variability found in a previous control group studied by us. The effect of IS-5-MN was significantly different ($p < 0.01$) from that found for spontaneous variability (Table III).

The effect of IS-5-MN on individual patients: In 21 patients, all the episodes of ischemia were eliminated, resulting in a curative rate of 75%. In 7 patients, the antiischemic effect was not satisfactory but there was a trend toward reduction in number and duration of ischemic episodes.

Angina pectoris: A comparison of anginal frequency between baseline phase (61 episodes week) and placebo phase (50 episodes week) showed no significant change ($p > 0.05$). Comparison between any of these 2 phases and IS-5-MN phase (8 episodes week) showed significant reduction ($p < 0.01$) in the active treatment (Fig. 5).

TABLE III Comparison of Effective Rate of IS-5-MN on Myocardial Ischemic Episodes with Spontaneous Variability Rate of Myocardial Ischemia

	Spontaneous Variability Rate (%)	Effective Rate of Elantan (%)	p Value
No. of ischemic episodes	33	88	<0.01
Duration of ischemia (min)	63	94	<0.01
Integration (mm/min)	41	95	<0.01
Total maximal ST segment (min)	37	86	<0.01

IS-5-MN = isosorbide mononitrate.

Change in heart rate and blood pressure: In the baseline phase the average heart rate was 80 beats/min, and systolic blood pressure was 120 mm Hg. In the placebo phase heart rate was 75 beats/min, and systolic blood pressure was 118 mm Hg. In the IS-5-MN phase, heart rate was 78 beats/min, and systolic blood pressure 116 mm Hg. Comparison between these 3 phases revealed no significant changes.

Adverse effects and tolerability: In the beginning of the IS-5-MN phase, 2 patients complained of thirst and 1 patient complained of vivid dreams. Headache was observed in 3 patients. These adverse effects were slowly decreased and well tolerated by the patients.

DISCUSSION

IS-5-MN is an active metabolite of the antianginal drug isosorbide dinitrate. It may be used as an independent drug and it has pharmacokinetic advantages over the parent molecule.[5,6] Previous studies have showed that IS-5-MN can effectively increase the work capacity in patients with angina pectoris.[7,8] In our study, IS-5-MN not only reduced the frequency of angina, but also effectively eliminated the episodes of any ischemia. After the IS-5-

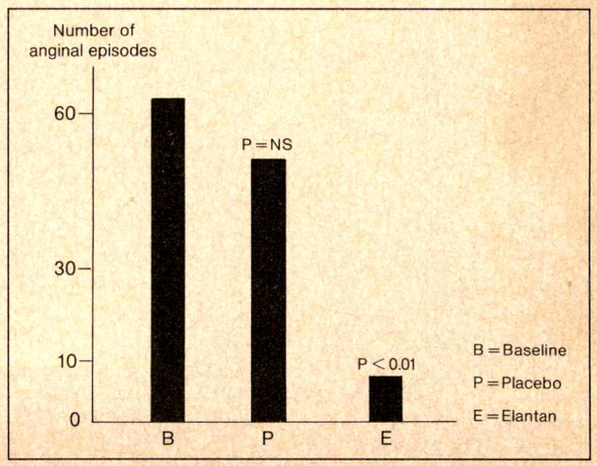


FIGURE 5. Number of anginal episodes before and after treatment. NS = not significant.

MN phase, in comparison with placebo phase, the total ischemia (painful + painless) in number, duration, integration and total maximal ST depression significantly decreased by 88, 94, 95 and 87%, respectively ($p < 0.01$). Furthermore, compared with placebo phase, the number, duration, integration and total maximal ST depression of silent myocardial ischemia also decreased by 88, 94, 96 and 87%, respectively ($p < 0.01$), thus demonstrating that IS-5-MN is an effective drug in the treatment of silent myocardial ischemia.

We found that in some patients, the number of ischemic episodes did not change greatly before and after medication, but duration of ischemia and integration of ST-segment deviation over time improved. Obviously, this demonstrates that the observation index for the curative rate using only the number of ischemic episodes is not sufficient. A more precise index is required. This report emphasized the need to apply the result of ST-segment depression multipled by duration (i.e., integration) as an observation index for curative effect in silent myocardial ischemia.

Our findings confirm the anti-ischemic efficacy of IS-5-MN in Chinese patients with silent myocardial ischemia.

REFERENCES

1. Cohn PF. Prognostic significance of asymptomatic coronary artery disease. *Am J Cardiol 1986;58:518–523.*

2. Stern S, Gavish A, Zin D, Tzivoni D. Clinical outcome of silent myocardial ischemia. *Am J Cardiol 1988;61:16F–18F.*

3. Schneeweiss A, Weiss M. Advances in Nitrate Therapy. *Berlin, Heidelberg, New York, London, Paris, Tokyo: Springer-Verlag, 1988:43–44.*

4. Schang SJ Jr, Pepine CJ. Transient asymptomatic ST-segment depression during daily activity. *Am J Cardiol 1977;39:396–402.*

5. Bidoggia JH, Casar JE, Hirschon AJ, Campo A, Nordaby R. Beneficial effects of isosorbide-5-mononitrate on exercise performance in patients with chronic stable angina pectoris. In: Cohn JN, Rittinghausen R, eds. Mononitrates. *Berlin: Springer-Verlag, 1985:201–214.*

6. Kamphausen U. Therapie mit Elantan in retardierter Form nach überstandenem Herzinfarkt. In: Hochrein H, Tauchert M, Schrey A, Weiss M, eds. Mononitrate. *München: Universitätsdruckerei und Verlag Dr C Wolf und Sohn, 1984:158–171.*

7. Krepp HP. Langzeitbehandlung der koronaren Herzerkrankung mit elantan long. In: Borchard U, Rafflenbeul W, Schrey A, eds. Mononitrate. *München: Universitätsdruckerei und Verlag Dr C Wolf und Sohn, 1985:176–183.*

8. Akhras F, Jackson G. Isosorbide-5-mononitrate as monotherapy in patients with chronic stable angina (abstr). *J Am Coll Cardiol 1986;7:230A.*

Prevention of Creatine Kinase-MB Release in Coronary Artery Disease and Pacing-Induced Myocardial Ischemia by Isosorbide Dinitrate Spray

Alon Marmor, MD, and Robert Klein, MD

The effect of isosorbide dinitrate (ISDN) spray on release of the isoenzyme creatine kinase-MB (CK-MB) after myocardial ischemia induced by atrial pacing was evaluated in 8 patients with coronary artery disease. Atrial pacing to ischemia (ST-segment depression of ≥1.5 mm for ≥80 ms) resulted in elevation of CK-MB levels in plasma drawn from the coronary sinus, from 1.8 ± 1.5 to 6.8 ± 7.0 ng/ml ($p < 0.001$) at 30 minutes after onset of ischemia. When atrial pacing was repeated at the same rate after 1 squirt of ISDN spray, 1.25 mg, the CK-MB levels were not altered despite significant ischemic ST-segment depression. It is concluded that ISDN prevents the process responsible for myocardial release of CK-MB, being either micronecroses or a reversible consequence of ischemia.

(Am J Cardiol 1990;65:36J–38J)

From the Cardiology Department, Rebecca Sieff Medical Center, Safed, Israel.

Address for reprints: Adam Schneeweiss, MD, Cardiovascular Research Foundation, Sauerberg 12, 6208 Bad Schwalbach 7, Federal Republic of Germany.

Elevation of the creatine kinase-MB (CK-MB) isoenzyme in the plasma of patients with ischemic heart disease has been established as a very sensitive and specific indicator of acute myocardial infarction.[1,2] However, in recent years evidence accumulated that elevated CK-MB with slightly elevated or normal total CK phosphokinase (CPK) is encountered in the context of angina pectoris (AP).[3,4] Our report in 1978,[5] as well as the recent report of White et al,[4] clearly points out that a subset of patients with unstable AP may have elevated CK-MB, when sequential enzymatic surveillance is conducted, regardless of the normal total CPK. Several other investigators[6–8] independently confirmed this observaton. The fact of elevated CK-MB in AP associated with normal or slightly elevated CPK, although accepted, is differently interpreted by different workers. Thus, Roberts et al[2] firmly believe that the presence of elevated CK-MB always indicted myocardial necrosis (subendocardial myocardial infarction), and silent myocardial ischemia, whereas other workers would include this entity in the realm of ischemia.[5,9–12]

Besides the theoretical aspects of scientific accuracy, this apparently semantic dilemma has obvious, important clinical implications. If elevated CK-MB represents necrosis, its prevention should be a therapeutic goal of every anti-ischemic therapy. If it represents reversible ischemia it might be an excellent indication as to the efficacy of anti-ischemic therapy. In a recent study we were able to demonstrate that plasma levels of CK-MB are elevated after pacing-induced ischemia in patients with coronary artery disease but not in human subjects with normal coronary arteries.[13]

This report presents our experience in preventing the release of CK-MB with isosorbide dinitrate (ISDN) in patients with coronary artery disease and myocardial ischemia induced by atrial pacing.

METHODS

Patients: Eight men (aged 52 ± 10 years [mean ± standard deviation]) with coronary artery disease documented by coronary angiography participated in the study. All had chronic stable exercise-induced angina pectoris. All signed an informed consent. Cardioactive drugs were discontinued in all patients 48 hours before the study.

Procedure: Right-sided cardiac catheterization was performed using a Zucker 7Fr bipolar pacing catheter

advanced from the internal jugular vein into the coronary sinus. The proximal electrode of the catheter was placed in the right atrium and its tip was placed, under fluoroscopy, in the coronary sinus. Continuous recording of intracardiac pressures and oxygen saturation during catheterization confirmed the positioning in the coronary sinus. The catheter allowed right atrial pacing and simultaneous blood sampling from the coronary sinus. A standard 12-lead electrocardiographic recording was obtained at rest and at each stage of atrial pacing. Pacing was terminated at 150 beats/min or at the development of horizontal or downsloping ST-segment depression of ≥1.5 mm for ≥80 seconds. Blood samples were obtained from the coronary sinus before initiation of pacing and at 10, 20 and 30 minutes after onset of the electrocardiographic ischemic changes. Blood samples were obtained simultaneously also from a peripheral vein. The procedure was repeated after ≥5 hours. At initiation of pacing, 1 squirt of ISDN spray (1.25 mg) was given. The rate of pacing was increased up to the rate achieved in the previous pacing period.

Enzymatic measurements: The blood samples were immediately centrifugated and frozen at −20°C and evaluated within 3 days of their being obtained. All measurements were performed in duplicate by laboratory technicians unaware of the patients' identity and diagnosis. Total CK was determined by Enzyline CK-Nac, a kinetic determination of CK activity after activation by N-acetylcisteine and expressed as IU/liter of serum. The Tandem CK-MB kits (Hybritec Europe SA) were used for measurements of CK-MB isoenzyme. By this method serum containing CK-MB isoenzyme reacts with a plastic bed (solid phase) that is coated with a monoclonal antibody directed toward an antigenic site on the M subunit of the CK-MB molecule and a second monoclonal antibody oriented toward an antigenic site on the B subunit of the same isoenzyme molecule. After the formation of the solid phase, CK-MB is washed out to remove the bound labeled antibody and then is incubated with an enzyme substrate. The concentration of CK-MB is calculated from the conventional spectrophotometric readings. The results are expressed in nanograms per milliliter. The issue of reproducibility of the elevation of enzyme levels in the coronary sinus after repeated cardiac pacing was addressed in a preliminary study.[13] An interval of 3 hours was found sufficient for reproducibility of the results. In the present study we used an interval of 5 to 24 hours.

Statistical analysis: Student paired *t* test was used to compare the changes in the enzyme levels in the same patients.

RESULTS

In all patients atrial pacing before treatment resulted in chest pain associated with ST-segment depression of 3.5 ± 0.5 mm. CK-MB in plasma obtained from the coronary sinus increased in all patients (Table I). Mean level increased from 1.8 ± 1.5 to 4.0 ± 3.4 ng/ml at 10 minutes after induction of ischemia, to 11.0 ± 11.8 ng/ml at 20 minutes and to 6.8 ± 6.9 ng/ml at 30 minutes ($p < 0.001$ at 20 and 30 minutes). When the procedure was repeated after ISDN spray the CK-MB levels in the coronary sinus were not significantly altered (Table I) despite the development of ST-segment depression (2.5 ± 0.4 mm) in all patients and chest pain in 4.

TABLE I CK-MB Levels in Coronary Sinus Before Pacing and at 10, 20 and 30 Minutes After Induction of Ischemia

Case	Before Pacing	Minutes 10	20	30
		CK-MB Baseline (ng/ml)		
1	4.2	9	5.2	5.4
2	0.4	5.2	24	4.9
3	0.1	1	8.5	9.8
4	0.6	0.7	51.5	6.7
5	5.4	5	11.2	11.5
6	2.1	6	12	7
7	6.5	2	14	12
8	1.2	3	8	3
Mean	1.8 ± 1.5	4.0 ± 3.4	11.0 ± 11.8	6.8 ± 6.9
		CK-MB After ISDN Spray (ng/ml)		
1	0.1	0.2	2	0.1
2	0.4	0.1	0.1	0.3
3	0.4	0.5	0.4	0.4
4	2	1.8	0.4	1.2
5	0.1	0	1	0.4
6	0.2	1	0.5	0.7
7	1.5	0.5	0.7	1
8	0.7	1.1	1	0.7
Mean	0.7 ± 0.7	0.6 ± 0.7	0.8 ± 0.6	0.6 ± 0.7

The total CK levels in the coronary sinus increased slightly from 35.7 ± 36.34 to 59.6 ± 64.4 ng/ml after pretreatment atrial pacing, and from 29.0 ± 30.9 to 41.1 ± 42.7 ng/ml ($p < 0.01$). The CK and CK-MB levels in peripheral blood were not significantly altered. No complications occurred during or after the study. No patient had clinical, electrocardiographic or enzymatic signs of acute myocardial infarction.

DISCUSSION

Our findings indicate that in patients with coronary artery disease ischemia induced by atrial pacing is associated with release of CK-MB from the myocardium, in the presence of slight but insignificant elevation of total CK in the coronary sinus but not in peripheral blood. This release can be prevented by ISDN.

Elevation of total CK after exercise was reported by numerous investigators.[7,8,12,13] In most of these studies no elevation of CK-MB was observed in healthy subjects or in patients. However, there are some reports mentioning a slight elevation in total CK and CK-MB isoenzyme after strenuous physical exercise in marathon runners.[12,14] The consensus about this phenomenon seems to be that the elevated CK in blood after a certain degree of exercise represents enzyme leakage from the skeletal musculature, which is paramount to the normal muscular activity and is proportional to the metabolic demands of the muscles, thus being a physiologic phenomenon. Few studies address the issue of the possibility of the release of total CK and CK-MB in exercise-induced ischemia. Klein et

al[15] found that no elevation in plasma CK-MB occurred in myocardial ischemia induced by treadmill exercise. Our previous studies[5,9] and the studies of Davis et al[8] reported a small but significant elevation of total CK and CK-MB in acute ischemic episodes induced by exercise. One of the most important arguments against the possibility of elevated CK-MB with normal total CK in peripheral blood was the fact that the release of small amounts of CK-MB from the heart may go undetected because of the dilution of this small amount of enzyme in the peripheral blood; the CK-MB elevations reported by us and others are probably artefacts. To clarify this topic, blood samples were obtained in this study simultaneously from the coronary sinus and peripheral veins.

Chong et al[16] reported in 1974 an elevation of total CK in coronary sinus after atrial pacing-induced myocardial ischemia. Similarly, Ninomiya et al[17] reported elevation in CK-MB isoenzyme in coronary sinus after very short episodes of acute coronary insufficiency (experimentally induced). All these studies including the present one clearly point toward the conclusion that some amount of CK-MB isoenzyme is released during myocardial ischemia into the coronary sinus, most of it being probably diluted in the peripheral blood. The general consensus in published reports is that elevation of CK-MB levels in blood above a certain percent of the total CK (usually 4%) indicates myocardial necrosis, and establishes the clinical diagnosis of acute myocardial infarction. In recent years several investigators advocated that elevated CK-MB may be found in entities resembling acute myocardial ischemia with reversible ST depressions and normal total CK, and some of them even suggested the possibility that irreversible cellular damage is not always necessary for the transmembranal passage of CK-MB into the blood. Although this is a view shared by a minority of workers, it cannot be easily disregarded after thorough histologic examination of the transiently ischemic myocardium in baboons failed to show any evidence of necrosis in the presence of elevated CK-MB.[10]

Regardless of the exact entity represented by elevation of levels of CK-MB in plasma from the coronary sinus, its prevention is definitely an essential goal of antiischemic therapy. If it represents myocardial necrosis, the accumulated damage should be prevented; if it results from reversible myocardial ischemia, it is an indicator of the consequences of the process. We have shown that ISDN spray can completely abolish the myocardial release of CK-MB associated with ischemia. This might have resulted from some suppression of the ischemia itself, because our patients had less ST-segment depression after ISDN administration. However, ST-segment depression even after ISDN administration was highly indicative of ischemia (2.5 ± 0.4 mm). This indicates a possible effect of ISDN on the specific process associated with the release of CK-MB itself.

REFERENCES

1. Wagner GS, Roe CR, Limbird LE, Rosati RA, Wallace AG. The importance of identification of myocardial specific isoenzyme creatine phosphokinase MB form in the diagnosis of acute myocardial infarction. *Circulation 1973;47:263–269.*

2. Roberts R, Gowda KS, Ludbrook KL, Sobel BE. Specificity of elevated serum MB creatine phosphokinase activity in the diagnosis of acute myocardial infarction. *Am J Cardiol 1975;36:433–437.*

3. Hong RA, Licht JD, Wei JY, Heller GV, Blaustein AS, Pasternak RC. Elevated CK-MB with normal total creatine kinase in suspected myocardial infarction: Associated clinical findings and early prognosis. *Am Heart J 1986; 111:1041–1047.*

4. White RD, Grande P, Califf L, Palmeri ST, Califf RM, Wagner GS. Diagnostic and prognostic significance of minimally elevated creatine kinase-MB in suspected acute myocardial infarction. *Am J Cardiol 1985;55:1476–1484.*

5. Marmor A, Alpan G, Keidar S, Grenadier E, Palant A. The MB isoenzyme of creatine kinase as an indicator of the severity of myocardial ischemia. *Lancet 1978;2:812–814.*

6. Yusuf S, Collins R, Lin L, Sterry H, Pearson M, Sleight E. Significance of elevated MB isoenzyme with normal creatine kinase in acute myocardial infarction. *Am J Cardiol 1987;59:245–250.*

7. Dillon MC, Calbreath DF, Dixon AM, Rivin BF, Roark SF, Ideker RE, Wagner GS. Diagnostic problem in acute myocardial infarction: CK-MB in the absence of abnormally elevated total creatine kinase levels. *Arch Intern Med 1982;142:33–38.*

8. Davies B, Watt DAL, Daggett A. Serum creatine kinase and creatine kinase MB isoenzyme responses of post-infarction patients after a graded exercise test. *Br Heart J 1983;50:65–69.*

9. Marmor A, Kahana L, Alpan G, Grenadier E, Keidar S, Palant A. Creatine kinase isoenzyme (CK-MB) in acute coronary ischemia. *Am Heart J 1979;97: 574–577.*

10. Heynricks JR, Amano J, Kenna T, Fallon JT, Patrick TA, Manders WT, Rogers JA, Rosendorf C, Vatner SS. Creatine kinase release not associated with myocardial necrosis after short periods of coronary artery occlusion in conscious baboons. *J Am Coll Cardiol 1985;6:1299–1304.*

11. Lott JA, Stang JM. Serum enzymes and isoenzymes in the diagnosis and differential diagnosis of myocardial ischemia and necrosis. *Clin Chem 1980; 26:1241–1250.*

12. Steele BW, Gobel FL, Nelson RR, Yasmineh WG. Creatine kinase isoenzyme activity following cardiac catheterization and exercise stress testing. *Chest 1978;73:489–492.*

13. Marmor A, Klein R, Plich M, Groshar D, Schneeweiss A. Elevated MB-CK isoenzyme after exercise stress test and atrial pacing in patients with ischemic heart disease. *Chest 1988;94:1216–1220.*

14. Kielblock AJ, Manjoo M, Booyens J, Katzeff IE. Creatine phosphokinase and lactic dehydrogenase levels after ultra long distance running. *S Afr Med J 1979;55:1061–1066.*

15. Klein MS, Weiss AN, Roberts R, Coleman R. Technetium-99m stannous pyrophosphate scintigrams in normal subjects, patients with exercise-induced ischemia and patiens with calcified valves. *Am J Cardiol 1977;39:360–367.*

16. Chong MA, West R, Parker JO. Myocardial balance of inorganic phosphate and enzymes in man: effects of tachycardia and ischemia. *Circulation 1974;49: 283–290.*

17. Ninomiya K, Hashida J, Geft I, Chaux E, Shell W, Fishbein MC, Rit J, Yano J, Ganz W. Brief repeat periods of ischemia have a cumulative effect and may cause myocardial necrosis (abstr). *Am J Cardiol 1981;47:445.*

A Dose-Finding Study of the Hemodynamic Effect of Isosorbide Dinitrate Spray in Congestive Heart Failure

Robert Klein, MD, and Tali Sharir, MD

A dose-finding study of the hemodynamic effect of a new formulation of isosorbide dinitrate (ISDN) spray was performed in 12 patients with chronic congestive heart failure. Doses of 1.25, 2.5, 5.0 mg and placebo, as 1 squirt, were randomly given to all patients. Hemodynamic measurements were performed by a Swan-Ganz catheter before and at 30 seconds and 1, 5, 10, 20 and 30 minutes after drug administration and every 30 minutes thereafter, until return of hemodynamic variables to baseline. Hemodynamic improvement evident as decreases in right-sided pressures and an increase in cardiac output was observed within 1 minute from administration of ISDN spray, and peaked at 5 minutes. Near maximal effect was achieved by the 2.5-mg dose. Thus, 2.5 mg of ISDN spray (new formulation) produces rapid, near-maximal hemodynamic improvement in patients with congestive heart failure.

(Am J Cardiol 1990;65:39J–42J)

From the Cardiology Department, Rebecca Sieff Hospital, Zefat, Israel.

Address for reprints: Robert Klein, MD, Cardiology Department, Rebecca Sieff Hospital, Zefat, Israel.

The most rapid conventional therapy for relief of symptoms in angina pectoris and dyspnea associated with heart failure is sublingual administration of nitrates in tablet form. However, even the rapidly acting sublingual tablets require a few minutes before onset of effect. Peak plasma levels are achieved about 2 minutes after dissolution of the tablet.[1] Moreover, the time required for dissolution of the tablet (which varies from patient to patient) further delays the onset of action. In elderly patients with a dry mouth this problem may be more pronounced.

Nitrate spray has been established as a form of rapid administration of nitrates in patients with angina pectoris, chronic congestive heart failure and pulmonary edema.[2–4] Nitroglycerin and isosorbide dinitrate (ISDN) sprays are available.[2,5] They have been shown to act as rapidly as, or even more rapidly than, sublingual nitrate tablets.

A new formulation of an ISDN spray in a hydrophilic solution with improved biovailability is now available. This report describes a dose-finding study of the hemodynamic effect of this new spray in patients with chronic congestive heart failure.

METHODS

Patients: Twelve patients (8 men and 4 women, aged 42 to 75 years [medium age 68]) were studied. All had chronic congestive heart failure for a period of ≥6 months. Ten of the patients were in New York Heart Association functional class III and 2 patients were in class II. The cause of heart failure was coronary artery disease in all cases. The inclusion criteria were: heart failure due to coronary, hypertensive or primary myocardial disease; heart failure of ≥6 months' duration; stable hemodynamic condition for ≥3 months before the trial; functional class II to III left ventricular filling pressure ≥18 mm Hg at rest; previous documented response to vasodilators; age 40 to 75 years; and left ventricular ejection fraction ≤35%, determined by radionuclide ventriculography or left ventriculography during cardiac catheterization. The exclusion criteria were: acute myocardial infarction within 3 months from trial; unstable angina pectoris or poorly controlled chronic stable angina pectoris; uncontrolled systemic hypertension; chronic obstructive pulmonary disease with pulmonary hypertension; life-threatening ventricular arrhythmias; artificial cardiac pacemaker; sick sinus syndrome; essential treatment with long-acting nitrates or other vasodilators; predomi-

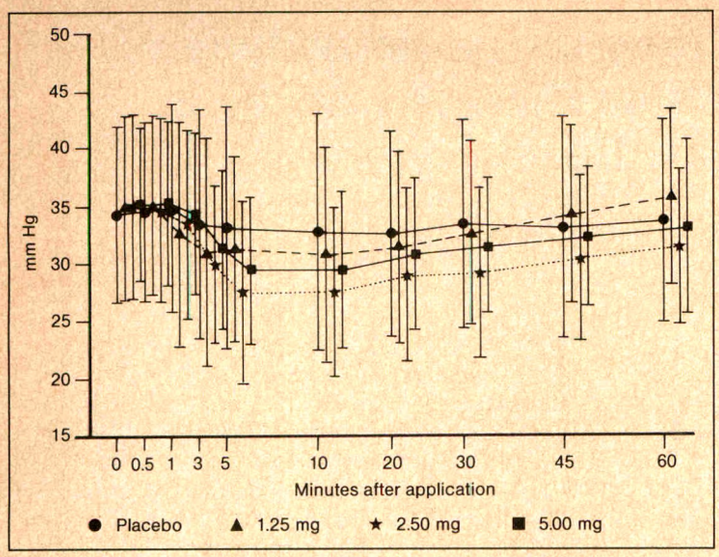


FIGURE 1. Mean pulmonary arterial pressure: changes over 1 hour with placebo and isosorbide dinitrate spray.

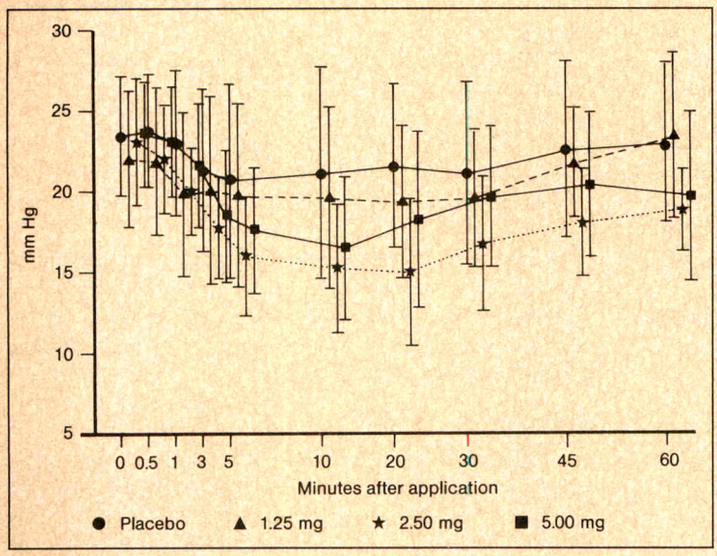


FIGURE 2. Pulmonary capillary wedge pressure: changes over 1 hour with placebo and isosorbide dinitrate spray.

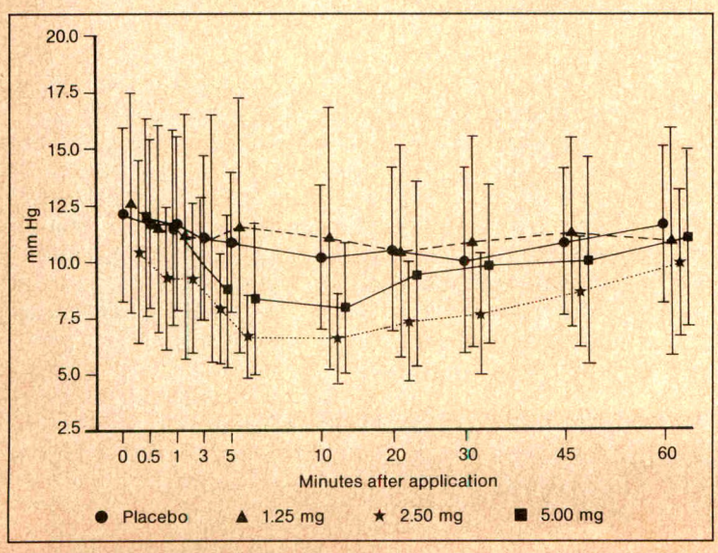


FIGURE 3. Right atrial pressure: changes over 1 hour with placebo and isosorbide dinitrate spray.

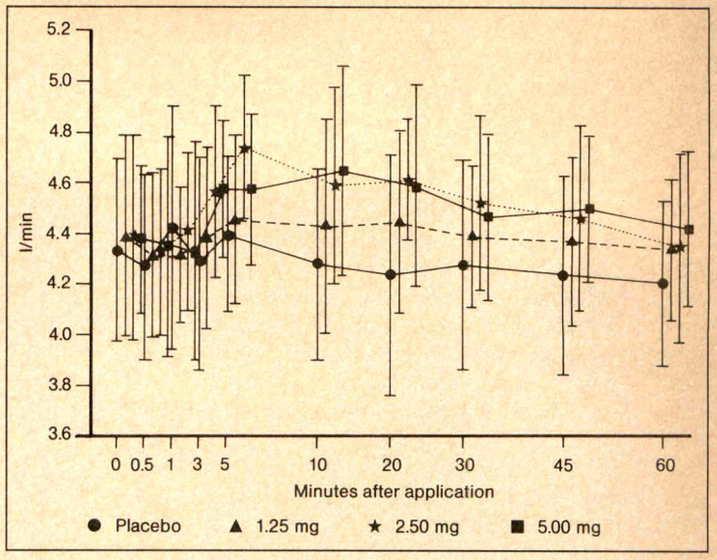


FIGURE 4. Cardiac output: changes over 1 hour with placebo and isosorbide dinitrate spray.

nant right heart failure with peripheral edema being the main sign of heart failure; cardiac valvar disease; any active pulmonary, systemic, hepatic, renal or metabolic disease; and mental impairment.

Study design: This was a randomized, double-blind, crossover, placebo-controlled dose-finding study. After screening procedures the patients were hospitalized in the cardiac unit. They received 1 squirt of a new formulation of an oral spray of ISDN (Schwarz Pharma, Monheim, Federal Republic of Germany) at a dose of 1.25, 2.5 and 5.0 mg, and placebo. After each dose, hemodynamic measurements were performed through a Swan-Ganz thermodilution catheter (inserted ≥12 hours before administration of the first dose) at 0.5, 1, 3, 5, 10, 20, 30, 45 and 60 minutes after administration, or for a longer period until return of the hemodynamic variables to the baseline level.

Analysis of data: The hemodynamic data were analyzed separately for each treatment of the study and compared with the control measurements of that day. A magnitude-time graph of activity was derived from the data for each day. Total activity of each treatment was measured by the difference integral to baseline. Confirmatory analysis was performed by 1-sided paired *t* tests using Bonferroni-adjusted p values. The multiple significance level was 5%. Exploratory data analyses were performed for heart rate and adverse reaction.

RESULTS

All patients completed the study. Placebo had no significant effect. In all, hemodynamic improvement, evident mainly as a reduction in pulmonary arterial, pulmonary capillary wedge and right atrial pressures and an increase in cardiac output, was observed after administration of the spray. A significant effect was observed at 1 minute after administration and peaked at 5 to 10 minutes, remained relatively stable between 10 and 20 minutes and declined thereafter (Fig. 1 to 5).

The hemodynamic effect of the 2.5-mg dose was near maximal and significantly greater than that of the 1.25-

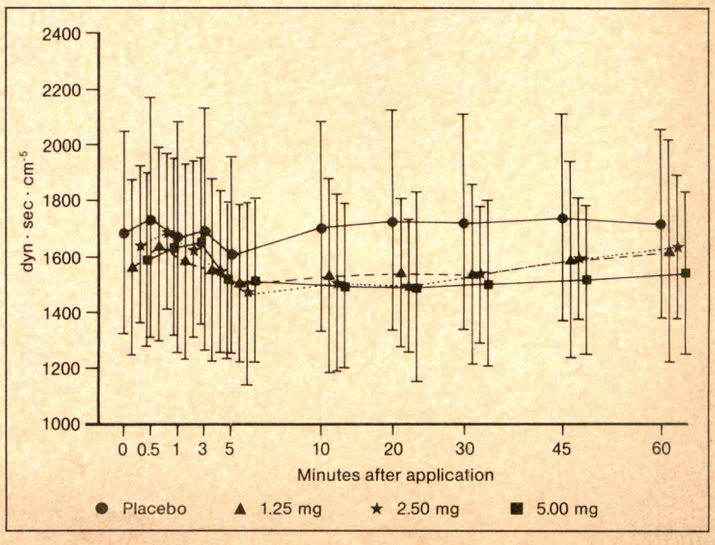


FIGURE 5. Systemic vascular resistance: changes over 1 hour with placebo and isosorbide dinitrate spray.

mg dose, which was not significant for all parameters in all time points where the effect of the 2.5 mg was significant. The 5.0-mg dose did not have a significantly greater effect than 2.5 mg.

No serious adverse effects were observed.

DISCUSSION

Our results confirm the rapid onset of action of the new formulation of ISDN spray in patients with chronic congestive heart failure. The new spray is similar to older formulations of nitroglycerin and ISDN spray.[1–3,6] The rapid onset of action and the fact that the patient does not have to hold the drug sublingually for several minutes make the spray an important alternative to sublingual administration of nitrate tablets.

This dose-finding study also confirmed that although some hemodynamic improvement is produced by 1.25 mg, the optimal dose is 2.5 mg. The effect of this dose is not significantly different from that of the 5.0-mg dose in time to onset, magnitude and duration of the effect.

Although sublingual tablet administration is considered the most rapid conventional method for relief of pain in angina pectoris and of dyspnea in congestive heart failure, its effect is not immediate and it has certain limitations. When given sublingually as tablets, nitrates reach peak plasma levels ≥2 minutes after dissolution of the tablet.[7] This time, however, shows marked interpatient variability. The dissolution process takes approximately 1 minute and it increases the time required to achieve peak plasma levels by approximately one half.

The dissolution time depends on numerous factors. It may be prolonged in the elderly, in regions with high temperatures and in patients with a dry mouth. Distressed patients with dyspnea or severe chest pain may find it difficult to hold the tablet under their tongues. In dependent patients the nurse has to follow the patients for several minutes until the tablet dissolves, and to take care that the drug will not be swallowed. These problems are avoided by the use of spray. Our findings with the new ISDN spray fulfill these expectations.

In conclusion, the new ISDN spray is an effective and safe short-term treatment for patients with chronic congestive heart failure. The optimal dose is 2.5 mg.

REFERENCES

1. Schneeweiss A. Nitroglycerin. In: Schneeweiss A, ed. Drug Therapy in Cardiovascular Diseases. *Philadelphia: Lea & Febiger, 1986:5–28.*

2. Reisin LH, Landau E, Darawshi A. More rapid relief of pain with isosorbide dinitrate oral spray than with sublingual tablets in elderly patients with angina pectoris. *Am J Cardiol 1988;61:2E–3E.*

3. Schneeweiss A, Marmor A, Plich M, Alpert JS. ISDN spray in comparing heart failure. *Am J Cardiol 1987;59:848–852.*

4. Wildfeurer A. Aspect pharmaceutische entwicklung eines neuen oralen ISDN spray. *Therapiewoche 1982;32:6141–6149.*

5. Parker JO, Vankoughnett KA, Farrell B. Nitroglycerin lingual spray: clinical efficacy and dose-response relation. *Am J Cardiol 1986;57:1–5.*

6. Marchionni N, De Bari M, Ferrucci L, Moschi G, Schneeweiss A. Comparative study of time-course of hemodynamic effect of isosorbide dinitrate spray and sublingual tablets in patients with pulmonary congestion. *Cardiovasc Drugs Ther 1988;2:529–532.*

7. Armstrong PW, Armstrong JA, Marks GS. Blood level after sublingual nitroglycerin. *Circulation 1979;59:585–588.*

Comparative Evaluation of a New Formulation of Isosorbide Dinitrate Oral Spray and Sublingual Nitroglycerin Tablets

Alon Marmor, MD

The magnitude and time course of the hemodynamic effect of a new formulation of an aqueous solution of isosorbide dinitrate (ISDN) spray were compared with those of sublingual nitroglycerin (NTG) tablets in 12 patients with chronic congestive heart failure. The patients received, in a random order, ISDN spray, 2.5 mg, or sublingual NTG, 0.8 mg. Hemodynamic measurements were performed before and at 1, 3, 5, 10, 20, 30 and 60 minutes after each drug. The second drug was given only after return of the hemodynamic parameters to baseline, plus a washout period of 2 hours. The hemodynamic variables measured were comparable at baseline. Both drugs produced hemodynamic improvement including a decrease in pulmonary capillary wedge pressure (PCWP), right atrial pressure and systemic and pulmonary vascular resistances. Only ISDN spray significantly increased cardiac output. The onset of action of ISDN spray was significantly more rapid than that of NTG. This was primarily evident in the decrease in PCWP. With ISDN spray the decrease started at 1 minute after administration, and at 3 minutes a decrease of 8.6 mm Hg was already found. The corresponding value for sublingual NTG was 1.6 mm Hg. The difference was highly significant ($p < 0.02$). The peak effect of ISDN spray on PCWP and right atrial pressure was greater than that of NTG.

Thus, the onset of the hemodynamic effect of the new formulation of ISDN spray is much more rapid than that of sublingual NTG tablets. At the doses used, the magnitude of the effect of the ISDN spray on some of the hemodynamic variables is greater than that of sublingual NTG.

(Am J Cardiol 1990;65:43J–45J)

From the Cardiology Department, Sieff Medical Center, Safed, Israel.
Address for reprints: Adam Schneeweiss, MD, Sauerberg 12, 6204 Bad Schwalbach 7, Federal Republic of Germany.

In acute administration of nitrates, emphasis is on the rapidity of onset of action. This is of importance in relieving pain in patients with angina pectoris or dyspnea in patients with pulmonary edema. Isosorbide dinitrate (ISDN) spray was shown to act very rapidly in these conditions. Its onset of action preceded that of sublingual tablets of ISDN in patients with angina pectoris,[1] acute deterioration of heart failure, chronic heart failure[2] and pulmonary congestion in the presence of normal cardiac output.[3] However, the spray was not compared with sublingual nitroglycerin (NTG) tablets, and it may be questionable whether these tablets would exert their onset of action as rapidly or even more rapidly than the spray. Because sublingual NTG tablets are the most rapid conventional way of administration of nitrates, every new nitrate formulation aimed at rapid onset of action should be compared with these tablets.

This report describes a comparative evaluation of the time course of the effect of a new formulation of an aqueous solution of ISDN spray with improved bioavailability and sublingual NTG tablets in patients with chronic congestive heart failure.

METHODS

Twelve patients (11 men and 1 woman, aged 62.7 ± 8.3 years [mean ± standard deviation]) with chronic congestive heart failure participated in the trial. All patients signed an informed consent before entering the trial. All had New York Heart Association functional class III (7 patients) or IIB (5 patients) heart failure due to coronary artery disease and a previous infarction (10 patients) or dilated cardiomyopathy (2 patients). In all cases heart failure was ≥6 months' duration, and the clinical condition was stable ≥3 months. All patients had a pulmonary capillary wedge pressure (PCWP) of 18 mm Hg at rest and left ventricular ejection fraction ≤35%.

All cardioactive drugs except for digitalis and orally administered diuretics were gradually reduced in dose, and completely discontinued at least 5 half-lives before the trial. Right-sided cardiac catheterization with a Swan-Ganz catheter was performed in the evening before the trial, and patients were allowed to rest until the morning.

On the morning of the trial, digitalis and diuretics were not given. Control hemodynamic measurements were obtained in the supine position. Thereafter, the patients received, in random order, either the new formulation of aqueous solution of ISDN oral spray, 2.5 mg, or a

TABLE I Hemodynamic Variables Before and at 1, 3, 5, 10, 20, 30 and 60 Minutes After Drug Administration

Time	HR (beats/min)	MAP (mm Hg)	PCWP (mm Hg)	RA (mm Hg)	CO (liters/min)	SVR (dynes s cm^{-1})
Isosorbide Dinitrate Spray						
0	83.5 ±11.3	94.2 ±5.8	25.7 ±5.4	13.6 ±3.2	3.7 ±0.3	1,741 ±170
1	84.7 ±6.0	93.5 ±8.9	24.0 ±4.6	13.3 ±3.4	3.8 ±0.3	1,694 ±210
3	92.2* ±2.8	86.7* ±6.0	17.1*,† ±2.5	9.1* ±2.3*	3.9 ±0.3	1,606*,† ±160
5	93.1* ±3.0	84.3* ±5.2	15.4*,† ±2.1	7.7* ±2.6	4.0 ±0.3	1,520*,† ±157
10	91.2* ±3.1	85.8* ±4.6	13.3*,† ±2.3	6.3*,† ±1.5	4.1* ±0.4	1,570* ±177
20	90.7* ±2.4	87.8* ±5.4	16.8* ±2.0	9.6* ±3.1	4.1* ±0.3	1,535* ±199
30	88.2 ±3.0	91.1 ±6.8	17.8* ±2.0	9.2* ±2.6	3.9 ±0.3	1,681 ±214
60	88.2 ±5.2	90.6 ±6.8	18.0* ±1.7	9.9 ±2.1	4.01 ±0.3	1,638 ±203
Sublingual Nitroglycerin						
0	82.4 ±11.9	95.3 ±6.4	25.4 ±4.9	14.2 ±3.2	3.7 ±0.3	1,765 ±200
1	82.8 ±7,2	92.6 ±5.8	25.0 ±4.8	13.8 ±3.3	3.7 ±0.3	1,703 ±144
3	87.2 ±6.3	92.5 ±7.6	23.8 ±6.0	11.9 ±3.2	3.7 ±0.3	1,768 ±206
5	88.5* ±4.2	89.4* ±7.8	20.7* ±6.6	10.7* ±3.7	3.8 ±0.3	1,681 ±188
10	93.1* ±3.8	86.2 ±4.4	18.9* ±4.5	9.7 ±3.7	3.9 ±0.3	1,568* ±175
20	92.0* ±3.5	87.6 ±5.5	18.3* ±4.5	9.5* ±3.7	3.9 ±0.3	1,608* ±169
30	90.3* ±2.8	89.4 ±6.2	18.9 ±3.5	9.7 ±2.7	3.8 ±0.2	1,674 ±164
60	88.0* ±4.8	91.7 ±6.7	22.1* ±3.4	12.4 ±3.2	3.8 ±0.4	1,695 ±213

* Significance of difference from baseline ($p < 0.05$).
† Significance of difference between isosorbide dinitrate spray and nitroglycerin ($p < 0.05$).
CO = cardiac output; HR = heart rate; MAP = mean systemic arterial pressure; PCWP = pulmonary capillary wedge pressure; RA = right atrial pressure; SVR = systemic vascular resistance.

sublingual NTG tablet, 0.8 mg. Hemodynamic measurements were repeated at 1, 3, 5, 10, 20, 30 and 60 minutes after administration, and every hour thereafter. After the hemodynamic variables returned to baseline an additional 2-hour washout interval was allowed. The second drug was then given and the process repeated.

The statistical significance of the findings was evaluated by the *t* test and analysis of variance.

RESULTS

All patients completed the trial. The pretreatment hemodynamic variables before administration of each drug were comparable (Table I). Both ISDN spray and sublingual NTG produced hemodynamic improvement, evident as a decrease seen in PCWP, mean pulmonary arterial pressure, right atrial pressure and systemic and pulmonary vascular resistances (statistically significant at $p < 0.05$). An increase in cardiac output was significant only with ISDN. The magnitude of the maximal effect on some of the hemodynamic variables was somewhat greater for ISDN spray than for nitroglycerin.

ISDN spray reduced PCWP from 25.7 ± 5.4 to 13.3 ± 2.3 mm Hg, and NTG reduced it from 25.4 ± 4.9 to 18.3 ± 4.5 mm Hg. The difference between the changes in pressures was statistically significant ($p < 0.05$). ISDN spray reduced right atrial pressure from 13.6 ± 3.2 to 6.3 ± 1.5 mm Hg, and NTG reduced it from 14.2 ± 3.2 to 9.5 ± 3.7 mm Hg ($p < 0.05$). The magnitude of the other hemodynamic changes was similar for both drugs.

The onset of action of ISDN spray was more rapid than that of sublingual NTG. This was primarily evident in the effect on PCWP. With ISDN spray the decrease in this pressure started at 1 minute after administration. At 3 minutes the wedge pressure was reduced by 8.6 mm Hg. With sublingual NTG the decrease in PCWP started only at 3 minutes and was, at that time, only 1.6 mm Hg. The difference was highly significant ($p < 0.02$). At 5 minutes, mean PCWP was reduced by 10.3 mm Hg with ISDN spray and by 4.7 mm Hg with sublingual NTG ($p < 0.05$). Systemic vascular resistance was reduced earlier and to a greater extent by ISDN spray than by sublingual NTG ($p < 0.05$). Heart rate was slightly but significantly increased and mean blood pressure was reduced with both drugs (Table I). No serious side effects or complications were observed.

DISCUSSION

This study revealed that the new formulation of ISDN spray produces the expected hemodynamic improvement, which is qualitatively similar to that produced by all other nitrates in patients with chronic heart failure. However, the onset of action of ISDN spray was more rapid than that of the fastest conventional mode of nitrate administration, namely, sublingual NTG tablets.

It may be argued that zero time for sublingual tablets in this study should be the end of dissociation and the beginning of absorption. From a clinical point of view, however, the important comparison is between time from administration to onset of action. Moreover, dissolution and absorption are continuous and overlapping processes.

Several previous studies have shown that an older formulation of ISDN spray acts fast and its onset of action is earlier than that of sublingual ISDN tablets.[1–3] This is most probably due to the more rapid absorption of the spray.[4] However, the question of whether the ISDN spray also acts more rapidly than sublingual NTG tablets remained unanswered. The present study confirms the superiority of the spray in this respect.

Another advantage of the spray found in this trial was the greater magnitude of the hemodynamic improvement, evident as greater decreases in left and right ventricular filling pressures and a greater decrease in systemic vascular resistance, compared with that produced by the sublingual NTG tablet. This finding is valid only for the doses used in the trial. However, 0.8 mg is in the higher range of sublingual NTG doses, whereas 2.5 mg is in the lower range of ISDN doses when this drug is given

sublingually. In any case, this point is only secondary, since the main advantage of the spray is in its more rapid onset of action.

Only ISDN spray significantly increased cardiac output. However, the increase was small and pretreatment cardiac output was only moderately reduced compared with normal values.

Both drugs slightly but significantly accelerated heart rate. Although a marked increase in heart rate is infrequent in patients with heart failure after administration of vasodilators, some increase may be observed. The rapid absorption of both NTG and ISDN could have contributed to this increase in our patients.

NTG lingual spray is also available. Doses of 0.4 and 0.8 mg of this spray were found effective in the treatment of angina pectoris.[5] In our study we demonstrated that the ISDN spray is superior to sublingual NTG. A comparative evaluation of both types of spray is required.

In conclusion, the new formulation of ISDN spray produces more rapid hemodynamic improvement than sublingual NTG tablets in patients with heart failure.

REFERENCES

1. Reisin LH, Landau E, Darawshi A. More rapid relief of pain with isosorbide dinitrate oral spray than with sublingual tablets in elderly patients with angina pectoris. *Am J Cardiol 1988;61:2E–3E.*

2. Schneeweiss A, Marmor A, Plich M, Alpert JS. ISDN spray in comparing heart failure. *Am J Cardiol 1987;59:848–852.*

3. Marchionni N, De Bari M, Ferruci L, Moschi G, Schneeweiss A. Comparative study of time-course of hemodynamic effect of isosorbide dinitrate spray and sublingual tablets in patients with pulmonary congestion. *Cardiovasc Drugs Ther 1988;2:529–532.*

4. Wildfeurer A. Aspect pharmaceutische entwicklung eines neuen oralen ISDN spray. *Therapiewoche 1982;32:6141.*

5. Parker JO, Vankoughnett KA, Farrell B. Nitroglycerin lingual spray: clinical efficacy and dose-response relation. *Am J Cardiol 1986;57:1–5.*

Randomized Double-Blind Comparison of Isosorbide Dinitrate and Nifedipine in Variant Angina Pectoris

Michael Aschermann, MD, Jan Bultas, MD, Debora Karetová, MD, Frantisèk Kölbel, MD, Michaela Kozáková, MD, and David Simper, MD

The antianginal and anti-ischemic effect of isosorbide dinitrate (ISDN), 120 mg once daily, and nifedipine, 20 mg twice daily, both in slow-release formulations, were compared in 17 patients with variant angina pectoris in a randomized, double-blind trial. The design included a placebo run-in period and two 6-week crossover periods of active treatment. Mean frequency of angina decreased significantly from 43 attacks per week during the placebo period to 4 per week with ISDN and 8 with nifedipine ($p < 0.001$). Sublingual nitroglycerin consumption decreased significantly from 37 tablets per week with placebo to 3 tablets per week with ISDN and 7 with nifedipine ($p < 0.001$). Both drugs reduced the silent and symptomatic ST-segment deviations on ambulatory electrocardiographic recording and increased maximal exercise tolerance. Episodes of coronary spasm could be provoked, by hyperventilation, in all patients during the placebo phase but in no patient during therapy with either active drug.

Thus, both ISDN and nifedipine, in their slow-release formulations, are effective in the treatment of variant angina pectoris.

(Am J Cardiol 1990;65:46J–49J)

From the First Medical Department, Second Medical Department and Third Medical Department, U nemocnice, Faculty of Medicine, Prague, Czechoslovakia

Address for reprints: Michael Aschermann, MD, Third Department of Medicine, U nemocnice 2, 128 21 Prague 2, Czechoslovakia.

Coronary artery spasm is an important cause of transient myocardial ischemia in some patients with angina pectoris and it may, in some cases, result in acute myocardial infarction.[1,2] Prinzmetal's variant angina was described in 1959[3] as chest pain at rest occurring at night or early morning and associated with ST-segment elevation which was reversible by nitrate administration. Prevalence of variant angina among all forms of angina pectoris is currently estimated to be 3 to 5%.[2] Previous experience showed that nitrates[4] and calcium antagonists[5–7] are especially effective in the treatment of patients with variant angina. Some double-blind studies suggested that nifedipine is superior to isosorbide dinitrate (ISDN),[8,9] others showed no difference in response to both drugs.[10] Nitroglycerin usually relieves the attacks and ISDN may prevent them. However, ISDN has a short half-life and must be taken several times daily. New slow-release ISDN, 120 mg, is effective for a 24-hour period. In this investigation we compared in a prospective, randomized, double-blind crossover fashion the efficacy of nifedipine to ISDN, 120 mg, in the treatment of patients with proved active variant angina.

METHODS

Patients: Seventeen patients (8 men and 9 women, aged 33 to 57 years) were prospectively entered into the study (Table I). Four patients withdrew from the study: 1 after the placebo period, 3 during the study. Criterion for patient inclusion was the clinical syndrome of chest pain associated with ST-segment elevations ≥0.1 mV. Reversible focal spasm (>75% luminal diameter narrowing from baseline) of an epicardial coronary artery was found either spontaneously (4 patients) or after provocation (13 patients). There was no evidence of hemodynamically important atherosclerotic coronary narrowing (defined as ≥50% reduction of luminal diameter after administration of nitroglycerin) in 13 patients. The remaining 4 patients had fixed hemodynamically important coronary artery stenosis. Patients were excluded from the study if they had recent myocardial infarction, congestive heart failure, serious arrhythmias and other serious medical problems. The use of long-acting nitrates, β blockers and calcium antagonists was prohibited during the study.

Study protocol: The study consisted of the 3 phases (Table II). Phase I was 1 week of placebo therapy. At the end of phase I all patients underwent clinical evaluation,

TABLE I Patients' Characteristics

Case	Age (yr) & Sex	Hyper-tension	DM	HLP	CAG	Spasm
1	44F	–	–	–	N	LAD
2	56F	–	–	–	N	LAD + LCX
3	45F	–	–	–	N	LAD
4	48F	+	+	+	75% LAD	RCA
5	48M	+	–	+	N	LAD
6	56M	+	–	–	N	LAD
7	45M	–	–	–	60% RCA	RCA
8	50F	–	–	–	70% RCA	RCA
9	51M	–	+	+	60% RCA	RCA
10	52M	–	–	–	N	LAD
11	33M	–	–	–	N	LAD
12	55M	–	+	+	N	LAD
13	47F	+	–	–	N	RCA
14	40M	–	+	+	N	RCA
15	54F	–	–	+	N	LAD
16	54F	–	–	+	N	LAD
17	57F	–	–	+	N	RCA

DM = diabetes mellitus; HLP = hyperlipoproteinemia; CAG = coronary angiography; N = normal finding; RCA = right coronary artery; LCX = left circumflex artery; LAD = left anterior descenders; + = present; – = absent.

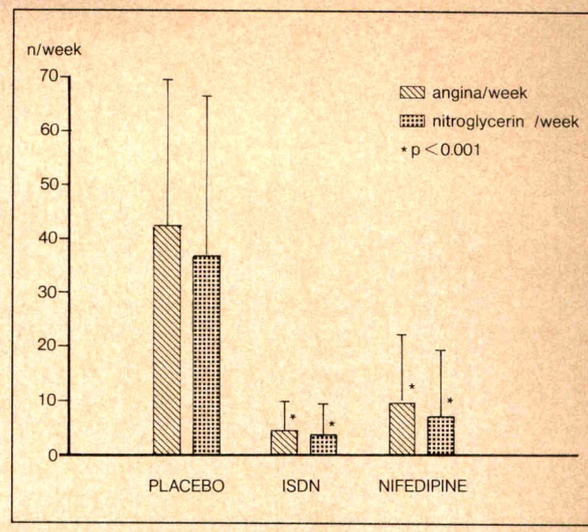


FIGURE 1. Anginal attacks and nitroglycerin consumption per week as recorded from patients' diaries.

exercise stress testing, spasm provocation using hyperventilation in combination with handgrip[2] and 24-hour Holter monitoring. Episodes of transient ST-segment shifts associated with either pain or silent ischemia and occurrence of arrythmias were detected. Transient ST-segment deviations from baseline were considered present if ST-segment elevations or depression >0.1 mV was present for ≥1 minutes. After the placebo phase, patients were randomized in a double-blind fashion either to therapy with nifedipine retard, 20 mg twice daily (Adalat Retard®), or ISDN, 120 mg once daily (Isoket 120®) for a 6-week period (phase II). After 6 weeks, patients were crossed over to the opposite drug treatment for a final 6 weeks (phase III). At the end of phases II and III all aforementioned tests were repeated. During the course of the study each patient maintained a written diary of chest pains and nitroglycerin usage. Prophylactic use of nitroglycerin was prohibited during all phases. Diary reviews and pill counts were used to monitor the patients' symptoms and compliance. All adverse effects were monitored on a regular basis and recorded. Adverse effects such as headache were treated symptomatically.

Data analysis: All patients' diaries and electrocardiographic recordings were analyzed by one of the investigators without knowledge of which pharmacologic agents were being administered. Each variable analyzed (chest pain, nitroglycerin use, ST-segment deviations, maximal tolerance during exercise stress testing, maximal working capacity during stress test) were compared for placebo, nifedipine and ISDN groups using paired *t* test. In all analyses, $p \leq 0.05$ was considered significant.

TABLE II Study Design*

Run-In Period	Placebo Period	Active Treatment	Wash-Out Period	Active Treatment
	1 Week	6 Weeks	2 Days	6 Weeks
	Placebo	ISDN 120 mg once daily Nifedipine 20 mg twice daily	Placebo	Nifedipine 20 mg twice daily ISDN 120 mg once daily
CAG Clinical evaluation Provocation Stress test Provocation Holter monitoring		Clinical evaluation Stress test Provocation Holter monitoring		Clinical evlauation Stress test Provocation Holter monitoring

Coronary angiography and spasm provocation during run-in period, clinical evaluations, stress testing, Holter monitoring and review of patients diaries after 1, 6 and 12 weeks.
ISDN = isosorbide dinitrate.

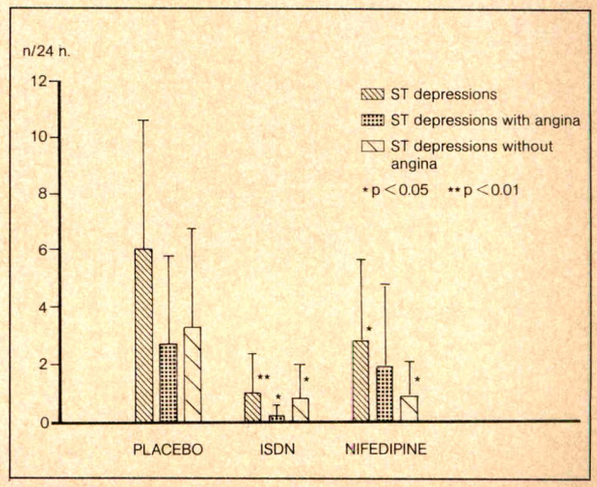


FIGURE 2. Number of ST-segment depressions with or without angina during 24-hour Holter monitoring. ISDN = isosorbide dinitrate.

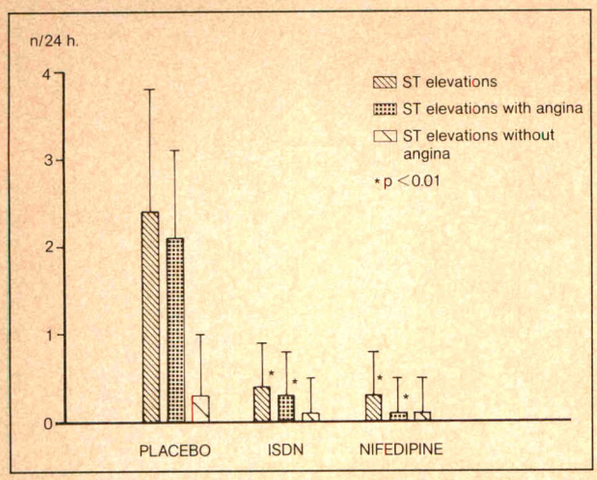


FIGURE 3. Number of ST-segment elevations with or without angina during 24-hour Holter monitoring. ISDN = isosorbide dinitrate.

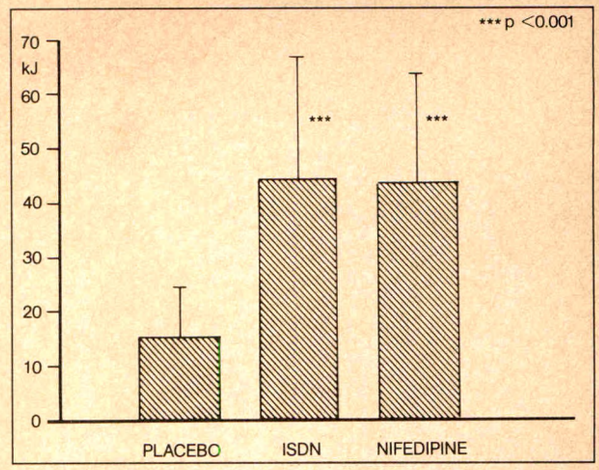


FIGURE 5. Maximal working capacity during stress test. ISDN = isosorbide dinitrate.

RESULTS

Clinical response to therapy and nitrate consumption (Fig. 1): Frequency of chest pain increased during the placebo phase from 25 to 43 attacks per week. Mean frequency of angina decreased significantly with both ISDN (4 episodes per week) and nifedipine (8 episodes per week) ($p < 0.001$). Consumption of nitroglycerin also decreased significantly from placebo phase (37 tablets per week) to the ISDN treatment (3 tablets per week) as well as nifedipine (7 tablets per week) ($p < 0.001$).

Holter monitoring data (Fig. 2 and 3): During both ISDN and nifedipine treatment phases the frequency of either symptomatic or asymptomatic shifts of ST segment was significantly decreased ($p < 0.001$) compared with the placebo phase. There was no difference between the ISDN and nifedipine groups.

Exercise stress testing (Fig. 4 and 5): Exercise stress testing performed after phases II and III in each group of patients showed significant increases in maximal tolerance during exercise as well as in maximal working capacity after both ISDN and nifedipine

Spasm provocation: Provocation of spasm was positive in all patients after the placebo phase. Repeated provocative tests after treatment phases II and III yielded negative results in all patients.

Adverse effects: The frequency of headache was greater with ISDN than with nifedipine. Five patients had headaches after ISDN (38.4%); in 3 patients (23.1%) headache was so severe that the study had to be terminated. Only 2 patients had slight headache during nifedipine treatment (15.4%). Other adverse effects often appearing during nifedipine treatment (pedal edema, dizziness) were not observed.

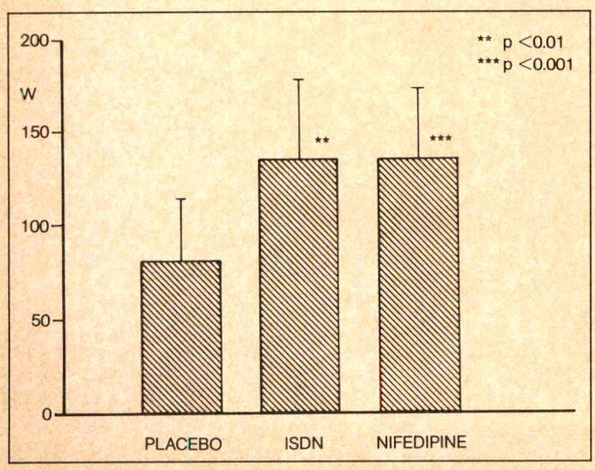


FIGURE 4. Maximal load tolerance during stress test. ISDN = isosorbide dinitrate.

DISCUSSION

Previous studies comparing antianginal effects of ISDN and nifedipine in patients with variant angina have been reported.[2,8,9] There is no general agreement as to whether one drug is more effective than the other. The study of Ginsburg et al[8] reported that nifedipine caused greater reduction in frequency of pain than ISDN (75 vs 61%). In contrast, Conti et al[2] and Hill et al[9] showed that neither drug seemed superior; some patients responded better to ISDN, others to nifedipine. Assessment of the drugs' efficacy in patients with variant angina presents some problems. In patients with variant angina, ST-segment shifts are not always associated with anginal pain (up to 60% of episodes).[10] This fact emphasizes the need for an objective method such as Holter monitoring.[11] Variant angina may also have spontaneous variations,[1] and clinical trials should include placebo periods long enough to detect them. In the study of Rizzon et al,[10] only 29 of 75 patients enrolled in their trial (38%) continued to experience episodes of angina at rest during the placebo phase. In our study, we found a significant increase in episodes of pain during the placebo phase with a concomitant increase in nitroglycerin consumption.

The results of our study show that both ISDN, 120 mg/day, and nifedipine, 20 mg twice daily, are compara-

ble in patients with variant angina. Symptomatic improvement was associated with documented decreases in symptomatic as well as asymptomatic ST-segment shifts in Holter monitoring data. The question is, could there be some advantage using isosorbide dinitrate instead of other nitrates? Recent studies have clearly showed that common therpeutic regimens using nitrates are often associated with diminished efficacy.[12] Tolerance develops rapidly and can be rapidly reversed during nitrate withdrawal. The use of intermittent or eccentric dosing with oral nitrates has been shown to maintain antianginal efficacy during long-term therapy. ISDN, 120 mg, provides lower plasma nitrate concentration during the terminal phase and can thus prevent development of tolerance. The main disadvantage with ISDN, 120 mg, is more frequent occurrence of intolerable headache. However, in >60% of our patients the antianginal effect of ISDN was very good without any adverse effect.

CONCLUSIONS

Our study showed the comparable efficacy of ISDN 120 mg/day, in a single dose and nifedipine, 20 mg twice daily, for the treatment of patients with variant angina in the active phase of the disease. Similar good results were observed when comparing the number of symptomatic or asymptomatic ST-segment shifts before and during treatment with both drugs. ISDN, 120 mg, appeared to be subjectively less well tolerated than nifedipine: headache with ISDN occurred more frequently and in 3 patients it was quite severe. ISDN, 120 mg/day, and nifedipine, 20 mg twice daily, may thus be considered first-choice therapy in the treatment of variant angina during phases of disease activity.

REFERENCES

1. Bultas J, Aschermann M. Variant Angina Pectoris. *Prague: Avicenum, 1988.* (*In Czech*)

2. Conti CR, Pepine CJ, Curry RJ Jr. Coronary artery spasm: an important mechanism in the pathophysiology of ischaemic heart disease. *Curr Probl Cardiol 1979;4:1–70.*

3. Prinzmetal M, Kennamer R, Merliss R, Wada T, Bor N. Angina pectoris I—a variant form of angina pectoris. *Am J Med 1959;27(2):375–383.*

4. Maseri A. A review of nitrate therapy in stable angina, variant angina, unstable angina and myocardial infarction. *Z Kardiol 1985;74:suppl 4:1–3.*

5. Gunther S, Green L, Muller JE, Mudge GH Jr, Grossman W. Prevention by nifedipine of abnormal coronary vasoconstriction in patients with coronary artery disease. *Circulation 1981;63:849–855.*

6. Hansen JF, Sandoe E. Treatment of Prinzmetal angina due to coronary artery spasm using verapamil: a report of three cases. *Eur J Cardiol 1978;7:327–335.*

7. Hugenholtz PG, Michels MR, Serryus PW, Brower RW. Nifedipine in the treatment of unstable angina, coronary spasm and myocardial ischemia. *Am J Cardiol 1981;47:163–173.*

8. Ginsburg R, Lamb IH, Schroeder JS, Bolen JL. Randomized double blind comparison of nifedipine and isosorbide dinitrate therapy in variant angina pectoris due to coronary artery spasm. *Am Heart J 1982;103:44–48.*

9. Hill JA, Feldman RL, Pepine CJ, Conti CR. Randomized double-blind comparison of nifedipine and isosorbide dinitrate in patients with coronary artery spasm. *Am J Cardiol 1982;49:431–438.*

10. Rizzon P, Scrutinio D, Mangini SG, d'Toma L. Randomized placebo controlled comparative study of nifedipine, verapamil and isosorbide dinitrate in the treatment of angina at rest. *Eur Heart J 1986;7:67–76.*

11. Cohn PR. Time for a new approach to management of patients with both symptomatic and asymptomatic episodes of myocardial ischemia. *Am J Cardiol 1984;54:1358–1359.*

12. Reichek N. Intermittent nitrate therapy in angina pectoris. *Eur Heart J 1989;10:suppl A:7–10.*

Intravenous Isosorbide-5-Mononitrate in the Treatment of Acute Myocardial Infarction

Dženana E. Rezaković, MD, PhD, Vladimir Goldner, MD, PhD, Zdravko Batinić, MD, Marija Weiss, DSc, Janez Štalec, and Leo Pavičić, MSc

The action of isorsorbide-5-mononitrate (IS-5-MN) infusion (range 6.0 to 10.0 mg/hour) was studied in 24 patients with and without acute heart failure (hemodynamic subsets I to IV) during acute myocardial infarction. Hemodynamic measurements were performed by right-sided cardiac catheterization. Intravenous IS-5-MN demonstrated significant hemodynamic effects compared with baseline values. In subsets I and II, a decrease in pulmonary wedge pressure (PWP) and in cardiac index (CI), without significant changes in heart rate, mean arterial pressure or systemic vascular resistance index were demonstrated. In subsets III and IV, a major increase in CI and a decrease in systemic vascular resistance index, as well as a decrease in PWP were found. Again no changes occurred in mean arterial pressure and heart rate. The dosage was similar in subsets I to IV (8.0, 7.9, 7.8 and 7.3 mg/hour); thus, the differences in the responses could not be attributed to dosage. It appears that several different patterns of hemodynamic IS-5-MN action exist, assuming that IS-5-MN operates on preload and afterload levels. The action of IS-5-MN mechanisms seems to be dependent on an initial hemodynamic subset. No patient had any deleterious hemodynamic effects. A decrease in CI in subsets I and II was not of clinical importance with these dosages. No nitrate tolerance during 9.0 hours of continuous therapy appeared. The duration of the time needed to restore baseline values after IS-5-MN discontinuation demonstrated the following: a decrease in CI in subsets I and II lasting an average of 2.2 hours; a decrease in PWP in subsets II and IV lasting an average of 4.2 hours; and an increase in CI in subsets III and IV maintained at an average of 3.8 hours. No signs of a rebound hemodynamic phenomenon were found in any patient.

(Am J Cardiol 1990;65:50J–56J)

From the Department of Medicine, University Hospital, Faculty of Medicine, Zagreb, Faculty of Sciences and Mathematics, Faculty of Kinesiology, University of Zagreb, Yugoslavia and Research and Development, Medical Department International, Schwarz Pharma AG, Monheim, Federal Republic of Germany.

Address for reprints: Dženana E. Rezaković, MD, PhD, 41000 Zagreb, Proleterskih Brigada 222/II, Yugoslavia.

Intravenous nitrates are widely accepted as early therapy for acute myocardial infarction to reduce infarct size and to improve ventricular performance.[1,2] However, opinions vary widely on the influence of nitrates on hemodynamic variables, especially on cardiac output and systemic arterial pressure.[3,4] Because these hemodynamic factors are essential for coronary perfusion and ventricular performance, the main task is to use the beneficial effects of nitrates and to prevent adverse hypotensive reactions. We undertook the study of nitrate mechanisms and investigated the relation of their action with the baseline hemodynamic status of each patient.[5]

Isosorbide-5-mononitrate (IS-5-MN) has been the last of the nitrates introduced for the treatment of acute myocardial infarction. It is considerably different from nitroglycerin and isosorbide dinitrate in its metabolism and excretion, resulting in insignificant interindividual differences in blood drug level and long elimination half-life (4.0 to 5.5 hours).[6] The therapeutic effects of IS-5-MN have since been well documented with regard to the treatment of coronary artery disease,[7–9] although little is known about its efficacy, especially in its intravenous form, in patients with acute myocardial infarction and acute heart failure.

The aims of this study were to: (1) investigate clinical and hemodynamic efficacy of intravenous IS-5-MN in the treatment of patients with and without acute heart failure during acute myocardial infarction; (2) test the hypothesis about different hemodynamic patterns of IS-5-MN action and its relation to initial patients' status in different hemodynamic subsets (I to IV); (3) assess if an attenuation of hemodynamic effects will occur after 7 to 9 hours of continuous IS-5-MN infusion; and (4) define the duration of hemodynamic effects after interruption of IS-5-MN infusion and potential occurrence of rebound phenomenon.

METHODS

Patients: The study comprised 24 patients (22 men and 2 women, average age 57.6 years [range 41 to 69]). Twenty-six patients with acute myocardial infarction were initially included but 2 patients withdrew.

The diagnosis of definite acute myocardial infarction was established according to World Health Organization criteria at admission to the coronary care unit.[10] Myocardial infarction in the anterior and inferior locations were found in 11 and 13 patients, respectively.

The patients in all hemodynamic subsets (I, II, III and IV) were included in the trial, i.e., with and without acute heart failure. Patients were randomly chosen on admis-

TABLE I Control and IS-5-MN Hemodynamic Values in Subsets I + II and III + IV

Variables	Control I + II	IS-5-MN I + II	Control III + IV	IS-5-MN III + IV
CVP	12.17 ± 3.60*	9.33 ± 1.93†	11.83 ± 2.85	9.50 ± 2.02†
PASP	38.00 ± 7.53	28.75 ± 3.81†	31.33 ± 6.76	25.67 ± 3.90†
PADP	19.50 ± 4.03	13.75 ± 1.83†	16.83 ± 3.76	13.58 ± 1.80†
PWP	21.33 ± 4.13	15.42 ± 1.60†	18.50 ± 3.88	14.75 ± 1.23†
HR	86.33 ± 14.67	90.75 ± 11.03	102.33 ± 8.68	102.42 ± 7.03
MAP	96.67 ± 9.58	92.83 ± 8.74	94.25 ± 12.10	93.08 ± 10.15
CI	2.66 ± 0.23	2.51 ± 0.26†	1.95 ± 0.20	2.43 ± 0.14†
SVRI	2,446.1 ± 269.9	2,674.4 ± 297.8	3,392.6 ± 513.1	2,764.9 ± 421.6†

* Arithmetic mean ± standard deviation; † $p < 0.01$ in multivariate analysis.
CI = cardiac index; CVP = central venous pressure; HR = heart rate; IS-5-MN = isosorbide-5-mononitrate; MAP = mean arterial pressure; PASP/PADP = pulmonary artery systolic/diastolic pressure; PWP = pulmonary wedge pressure; SVRI = systemic vascular resistance index.

sion to the coronary care unit according to clinical signs of pulmonary congestion and peripheral hypoperfusion as well as to hemodynamic values of pulmonary wedge pressure (PWP) and cardiac index (CI). Hemodynamic subsets were determined according to Forrester's classification[11]: subset I—PWP ≤18 mm Hg, CI >2.2 liters/min/m^2; subset II—PWP >18 mm Hg, CI >2.2 liters/min/m^2; subset III—PWP ≤18 mm Hg, CI ≤2.2 liters/min/m^2; subset IV—PWP >18 mm Hg, CI ≤2.2 liters/min/m^2. The patients with angina pectoris persisting after sublingual nitroglycerin were included in hemodynamic subset I. All patients gave informed consent.

Exclusion criteria were: systolic arterial pressure <100 mm Hg; heart rate >120 and <55 beats/min; significant arrhythmia requiring intervention (supraventricular or ventricular tachycardia, ventricular fibrillation, heart block requiring pacemaker); hypertension >180/110 mm Hg; preexisting valvular heart disease; mechanical complications (pericardial effusion or constriction); pulmonary obstructive disease; cardiomyopathy; age >70 years; β-adrenergic blocking therapy administered within 48 hours; and acute intercurrent disease.

Two patients, being initially in subset IV, withdrew at 1 to 3 hours after the beginning of the study because of clinical and hemodynamic deterioration with an interruption of IS-5-MN administration and introduction of resuscitation. Both patients died, the first because of ventricular fibrillation and the other because of cardiogenic shock. An autopsy confirmed the ventricular aneurysm that had been assessed during a previous myocardial infarction 5 years ago.

Two patients who had successfully completed the IS-5-MN trial died, the first after 10 hours because of ventricular rupture and the other after 20 hours because of ventricular fibrillation.

Study design: This open trial was approved by the hospital committee on human research. Patients were included in the study immediately on admission to the coronary care unit. Baseline control hemodynamic parameters were measured 3 times over 45 minutes to confirm a stable status and to determine hemodynamic subset.

A titration period was begun with 1.0 mg/hour of IS-5-MN infusion, with an added dose of 2.0 mg/hour every half hour. When hemodynamic values approached prestated criteria of IS-5-MN efficacy, the dosage was elevated by 1.0 mg/hour and a continuous infusion was begun at a fixed dose. Titration period lasted 2.0 to 3.0 hours with hemodynamic measurements obtained every half hour. Infusion period continued over 5.5 hours (range 6.0 to 10.0 mg/hour of IS-5-MN), with measurements obtained each hour. IS-5-MN infusion was not interrupted during titration and infusion periods, i.e., during 7.5 to 9.0 hours, with an augmented dose during the titration period and a fixed IS-5-MN dose over the infusion period. Infusions were performed with an infusion pump through standard intravenous sets.

Before beginning the study, a small pilot study composed of 5 patients confirmed that an intravenous IS-5-MN dosage could be safely augmented by 2.0 mg/hour each half hour, because augmentation of dosage by 1.0 mg/hour was too slow and not effective enough.

Optimal IS-5-MN dosage administered over the infusion period was determined during the titration period on the basis of the following end points: a disappearance or significant attenuation of angina pectoris in subset I; a decrease of elevated PWP at 16 to 18 mm Hg or an increase in low CI ≥15% or >2.2 liters/min/m^2; a 10%

TABLE II Analysis of Differences Between Control (C) and IS-5-MN Hemodynamic Values in Subsets I + II and III + IV

Variables	C—IS-5-MN (I + II) $\bar{X}$	C—IS-5-MN (I + II) Discriminant Function	C—IS-5-MN (III + IV) $\bar{X}$	C—IS-5-MN (III + IV) Discriminant Function
CVP	−2.83	−0.18	−2.33	−0.13
PASP	−9.25	−0.28	−5.67	−0.16
PADP	−5.75	−0.35	−3.25	−0.14
PWP	−5.92	−0.32	−3.75	−0.14
HR	4.42	0.11	0.08	0.01
MAP	−3.83	−0.11	−1.17	−0.03
CI	−0.15	−0.36	0.48	0.29
SVRI	128.23	0.11	−627.71	−0.21
$DF_1 = 8$	F = 24.35		F = 34.80	
$DF_2 = 4$	MD = 44.65		MD = 63.80	
	$p < 0.01$		$p < 0.01$	

Nonunderlined correlation coefficient = not significant; underlined correlation coefficient = $p < 0.01$. DF = degree of freedom; F = F-test value; MD = Mahalanobis distance. $\bar{X}$ = arithmetic mean of differences between control and IS-5-MN values; other abbreviations as in Table I.

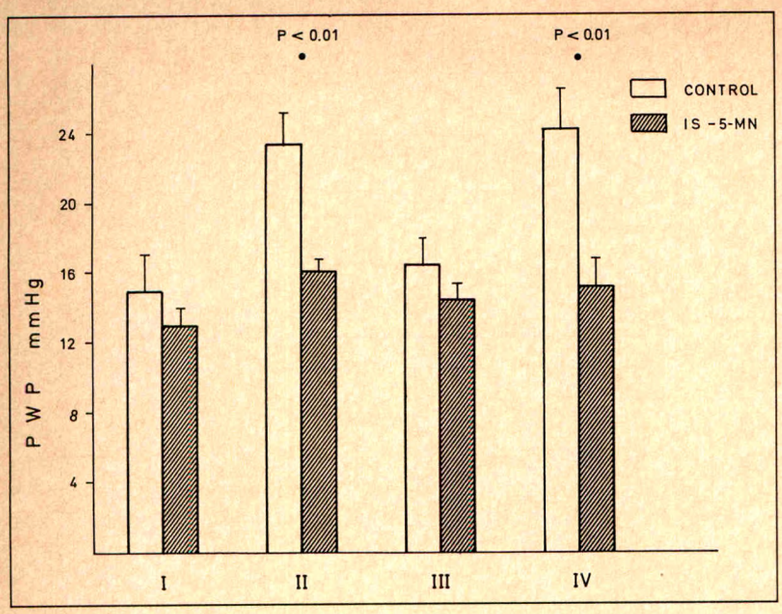


FIGURE 1. Pulmonary wedge pressure (PWP): initial and isosorbide-5-mononitrate (IS-5-MN) values in subsets I to IV. *p <0.01 compared with initial values.

decrease in mean arterial pressure; a 10% decrease in normal and 30 to 40 mm Hg in elevated systolic arterial pressure but not <90 mm Hg; an increase in heart rate ≤20 beats/min and a decrease not <50 beats/min.

After the IS-5-MN infusion period, nitrate administration was terminated and 5% glucose infusion was continued with hemodynamic measurements obtained each half hour. This period after IS-5-MN administration lasted a maximum of ≤4.5 hours in a case in which either hemodynamic values approached baseline results sooner or any clinical or hemodynamic deterioration occurred. After this period terminating the trial, the patients' treatment was continued with either IS-5-MN or other medication depending on actual indication.

All hemodynamic measurements were performed twice in a standardized manner by a physician to improve the accuracy and reproducibility of the results, which were finally calculated as a mean of at least 2 values in each time period.

Patients were not given any other drug during IS-5-MN hemodynamic investigation, except previous or newly started antiarrhythmic or anticoagulant therapy. Long-acting nitrates and calcium antagonist therapy were terminated within 6 to 12 hours and diuretics 4 to 6 hours before the beginning of the trial.

At the beginning of the investigation, only sublingual nitroglycerin, 0.5 mg, could be administered for persisting angina. The first hemodynamic measurement was obtained ≥30 minutes after initiation of therapy.

If hemodynamic effects during IS-5-MN infusion were considered clinically unfavorable, the study was discontinued and other vasodilator and inotropic therapy

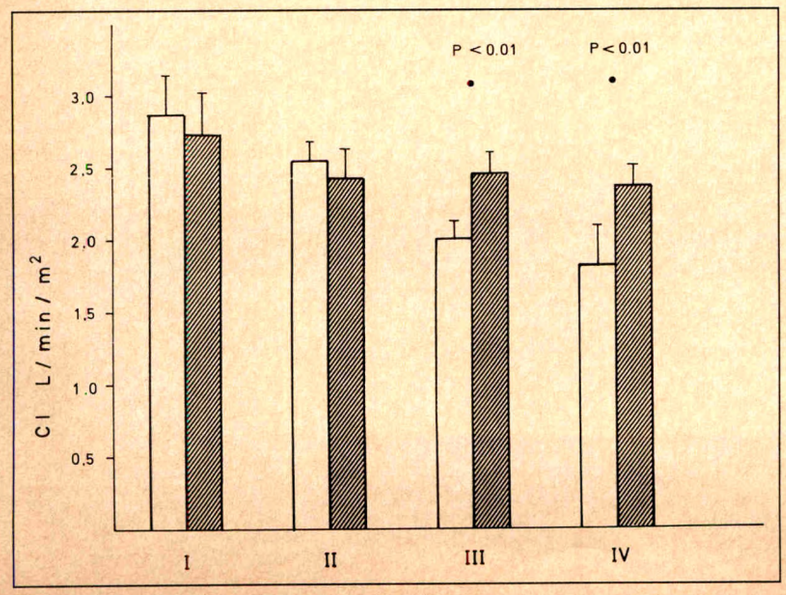


FIGURE 2. Cardiac index (CI): initial and isosorbide-5-mononitrate (IS-5-MN) values in subsets I to IV. *p <0.01 compared with initial values.

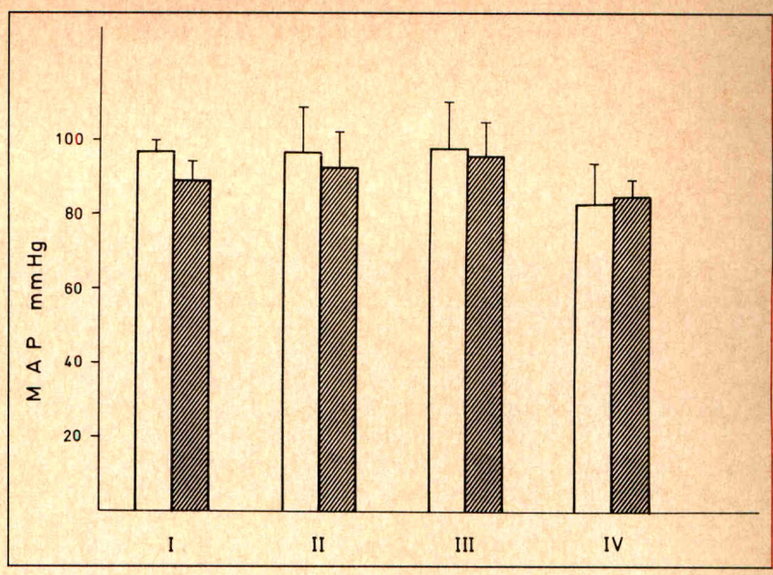


FIGURE 3. Mean arterial pressure (MAP): initial and isosorbide-5-mononitrate (IS-5-MN) values in subsets I to IV. p <0.01 compared with initial values.

begun. The adverse effects included an increasing severe angina pectoris, an increase in PWP by 20%, a decrease in CI >10%, a decrease in systolic arterial pressure <90 mm Hg, a decrease in mean arterial pressure >10% or <80 mm Hg, and either marked tachycardia or bradycardia.

All patients underwent continuous electrocardiographic monitoring, as well as creatine kinase activity measurements, repeated serially every 3 hours.

Experimental procedures: The trial was conducted in the coronary care unit. A flow-directed thermodilution catheter was inserted in the pulmonary artery under waveform monitoring control by a percutaneous approach to the right subclavian vein after local anesthesia with lignocaine 2%. All pressures were measured with the zero reference point at axillar line. Systemic arterial pressure was measured by insertion of the cannula to the radialis artery. The pressures (mm Hg) and cardiac output (liters/min) were monitored by a Hewlett-Packard computer with central station that registered all hemodynamic parameters and demonstrated their trends over time. The following hemodynamic values were measured: heart rate, systolic/diastolic/mean arterial pressures, central venous pressure, pulmonary systolic/diastolic/mean artery pressures, PWP and cardiac output. The values of CI (liters/min/m^2) and systemic vascular resistance index (dynes s cm^{-5}/m^2) were calculated.

Statistics: Statistical analysis of the quantitative and qualitative changes during IS-5-MN administration was performed by one of the analyses for repeated measurements, the model of differences based on the analysis of the matrix of differences. In this analysis each subject serves as his/her own control. This model is a multivari-

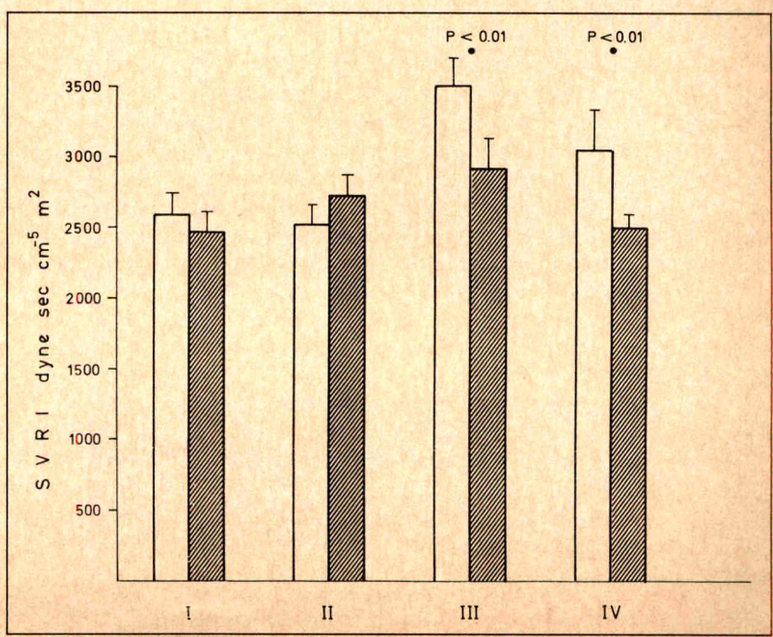


FIGURE 4. Systemic vascular resistance index (SVRI): initial and isosorbide-5-mononitrate (IS-5-MN) values in subsets I to IV. *p <0.01 compared with initial values.

TABLE III Control and Hemodynamic Values After IS-5-MN in Subsets I + II and III + IV

Variables	Control I + II	After IS-5-MN I + II	Control III + IV	After IS-5-MN III + IV
CVP	12.67 ± 3.60*	11.00 ± 2.89	11.83 ± 2.85	10.17 ± 2.82
PASP	38.00 ± 7.53	35.83 ± 7.19	31.33 ± 6.76	29.33 ± 5.68
PADP	19.50 ± 4.03	17.58 ± 3.50	16.83 ± 3.76	16.08 ± 2.87
PWP	21.33 ± 4.13	19.50 ± 3.75	18.50 ± 3.88	17.50 ± 3.57
HR	86.33 ± 14.67	90.17 ± 9.30	102.33 ± 8.68	102.67 ± 9.37
MAP	96.67 ± 9.59	96.25 ± 8.01	94.25 ± 12.10	91.92 ± 10.88
CI	2.66 ± 0.23	2.56 ± 0.21	1.95 ± 0.19	2.03 ± 0.14

* Arithmetic mean ± standard deviation.
Abbreviations as in Table I.

ate analysis testing the significance of changes before and during therapy in the space of all examined hemodynamic variables and for each one of them.[12,13] The significance of the statistical analysis was determined at $p < 0.01$.

RESULTS

Analysis of differences during IS-5-MN infusion in patients in hemodynamic subsets: Analyses of differences were performed in 12 patients each (subsets I + II and III + IV) to test potential differences in hemodynamic IS-5-MN effects depending on different initial subsets. The patients in subsets I and II (3 and 9 patients) were treated together because they had normal CI and normal or elevated PWP, whereas the patients in subsets III and IV (9 and 3 patients) were treated as 1 group because of low CI and normal or elevated PWP. This was done because the patient sample in each hemodynamic subset was not large enough to permit multivariate analysis.

The analysis of differences in subset I + II showed that IS-5-MN had significant hemodynamic effects compared with control values. This was demonstrated by a decrease in PWP, pulmonary artery pressures, central venous pressure and in CI; however, there were no significant changes in heart rate, mean arterial pressure or systemic vascular resistance index (Tables I and II, Fig. 1 to 4).

The analysis of differences in subset III + IV showed that IS-5-MN also had significant hemodynamic effects compared with control values. These changes were related to a major increase in CI, as well as a decrease in systemic vascular resistance index, PWP, pulmonary artery pressures and central venous pressure. However, there were no significant changes in mean arterial pressure and heart rate (Tables I and II, Fig. 1 to 4).

Analysis of differences after IS-5-MN infusion in patients in hemodynamic subsets: Analysis of differences in the period after IS-5-MN administration compared with baseline results was performed with values obtained 3.5 to 4.5 hours after the termination of nitrate infusion. These analyses showed no significant overall hemodynamic effects compared with control results in subsets I + II and III + IV (Tables III and IV).

However, some IS-5-MN effects were still present in individual parameters when analyzing patient sheets. The analysis of the duration of the time needed to restore baseline hemodynamic values in each patient after IS-5-MN discontinuation demonstrated the following: a decrease in CI in subsets I and II lasted an average 2.2 hours (range 0 to >4.0); a decrease in PWP in subsets II and IV lasted an average 4.2 hours (range 2.5 to >4.0); and an increase in CI in subsets III and IV was maintained an average 3.8 hours (range 2.0 to >4.0).

No sign of a rebound hemodynamic phenomenon occurred in any patient in the postinfusion period.

No serious adverse effects appeared during the trial and patients' tolerability was mainly good; flushes, sweating, headache or nausea occurred in 14 patients without any objective or subjective indication to discontinue or interfere with IS-5-MN therapy.

DISCUSSION

This study showed significant and different IS-5-MN hemodynamic effects in patients in hemodynamic subsets I to IV during acute myocardial infarction. Mean values of IS-5-MN dosage administered during infusion were similar for subsets I, II, III and IV (8.0, 7.9, 7.8 and 7.3 mg/hour), so the differences in hemodynamic responses can not be attributed to dosage but to different mechanisms of IS-5-MN action.

Several patterns of IS-5-MN hemodynamic mechanisms supposedly exist: the effects on preload (a decrease in elevated PWP) and on afterload (an increase in decreased CI and a decrease in augmented systemic vascular resistance). However, which hemodynamic mechanism will operate depends on the pattern of initial hemodynamic disturbance. This assumption explains that a decrease in CI in subsets I and II depends on a reduction in PWP (i.e., left end-diastolic filling pressure) and that an increase in CI in subsets III and IV is related to a decrease in systemic vascular resistance. The quantity of these changes appears to be related proportionally to the magnitude of initial hemodynamic disturbance.

These analyses of patient subsets demonstrated variety of pathophysiologic hemodynamic responses. They are undetectable in the analysis of mixed patient samples. In the trials with heterogeneous patient samples including different hemodynamic subsets, findings are mainly dependent on the sample itself, i.e. on random hemodynamic mechanisms dominating in the response. This could be an answer to conflicting and different findings in many hemodynamic studies of nitrates.

During the titration and infusion periods of 7.5 to 9.0 hours of IS-5-MN therapy with increasing and fixed dosage, no signs of attenuation of achieved effects occurred. On the contrary, in most of the patients, symptomatic relief and hemodynamic responses improved from the beginning until the end of the infusion period with fixed IS-5-MN dosages.

Global clinical assessment demonstrated intravenous IS-5-MN therapy as efficacious since symptoms of angina pectoris, dyspnea, fatigue, and so forth, disappeared or attenuated and all patients with acute heart failure were assessed to be in hemodynamic subset I at the end of IS-5-MN infusion. No patient developed any deleterious hemodynamic effects or symptomatic deterioration except 2 patients who withdrew from the study. A decrease in CI in patients in subsets I and II was not of clinical importance with this dosage. However, it is reasonable to recommend the titration of the lowest IS-5-MN dosage in these subsets to produce satisfactory symptomatic and hemodynamic results without potential adverse effects.

These data demonstrated high interindividual variability in sustaining hemodynamic responses after termination of IS-5-MN infusion. Since elimination half-life of intravenous IS-5-MN is approximately 4 hours, these data are very important for clinical decisions and prediction of hemodynamic situations after interruption of IS-5-MN therapy. Beneficial hemodynamic effects on PWP and CI are maintained for a considerably longer time (mean 4.2 and 3.8 hours) than a decrease in CI (2.2 hours). Finally, no sign of rebound hemodynamic phenomenon appeared in any patient.

These results are mainly supported by few other studies with IS-5-MN therapy in patients with acute heart failure. Gammage et al[14] showed a significant decrease in PWP and CI without a change in arterial pressure after bolus of IS-5-MN in patients with acute heart failure (subset II) during acute myocardial infarction. Rabinowitz et al[15] demonstrated a significant decrease in PWP, an increase in stroke work index, and a slight, insignificant increase in CI with only minimal decrease in systemic vascular resistance in patients with acute heart failure (subset IV), whereas a significant decrease in PWP and an increase in CI associated with a decrease in elevated systemic vascular resistance was seen in patients with chronic heart failure. Harf and Welter[16] showed significant symptomatic improvement in patients with pulmonary edema with IS-5-MN infusion. All these investigators showed that IS-5-MN effects could be maintained with infusion or oral therapy from 24 to 48 hours without any adverse decrease in blood pressure. Similar results were obtained by Lehmann and Polensky,[17] who confirmed different effects of oral IS-5-MN in patients with and without acute heart failure (subset III and IV) during acute myocardial infarction; in the former it induced a reduction and in the latter an increase in CI and arterial pressure, indicating different actions. They demonstrated that no change in CI could be seen when analyzing the group as a whole, and concluded that such a result is due to the heterogeneity of the sample, because when a sample is homogeneous the differences are significant. This supports our assumption that IS-5-MN effects depend on initial hemodynamic status; however, such effects can be demonstrated only in a defined sample of treated patients.[5]

TABLE IV Analysis of Differences Between Control (C) and Hemodynamic Values After (P) IS-5-MN in Subsets I + II and III + IV

	C—P IS-5-MN (I + II)		C—P IS-5-MN (III + IV)	
Variables	$\bar{X}$	Discriminant Function	$\bar{X}$	Discriminant Function
CVP	−1.17	−0.30	−1.67	−0.47
PASP	−2.17	−0.55	−2.00	−0.49
PADP	−1.92	−0.44	−0.75	−0.25
PWP	−1.83	−0.56	−1.00	−0.48
HR	3.83	0.17	0.33	0.02
MAP	−0.42	−0.06	−2.33	−0.19
CI	−0.10	−0.53	0.08	0.34
$DF_1 = 7$	F = 3.83		F = 3.34	
$DF_2 = 5$	MD = 4.10		MD = 4.29	
	p >0.01 (NS)		p >0.01 (NS)	

$\bar{X}$ = arithmetic mean of differences between control and values after IS-5-MN administration.
NS = not significant; other abbreviations as in Tables I and II.

There also are few trials with IS-5-MN in patients with chronic heart failure. Schneeweiss[18] showed that intravenous IS-5-MN and nitroglycerin produced similar effects in a reduction of PWP and an increse in CI. However, nitroglycerin had greater influence on the reduction in systolic and mean blood pressures, as well as systemic vascular resistance compared with results from IS-5-MN administration. Schneeweiss concluded that IS-5-MN may be safer in patients with heart failure of ischemic etiology because it is less likely to produce excessive hypotension and to lower coronary perfusion. Hutton et al[19] showed the advantage of intravenous IS-5-MN compared with intravenous frusemide. Although frusemide provoked a decrease in CI and stroke volume with unchanged PWP in the first 60 minutes after administration, IS-5-MN significantly reduced PWP within 5 minutes, and despite a reduction in systolic arterial pressure, cardiac output was maintained. The investigators concluded that intravenous IS-5-MN may play an important role in the therapy of patients with acute heart failure to counteract the acute vasoconstriction of frusemide.

These results support the assumption that IS-5-MN affects preload and afterload as does arterial and venous vasodilators. Based on our results, the action of different IS-5-MN mechanisms as well as its magnitude are considered dependent on initial hemodynamic subsets underlying acute heart failure. This assumes a dynamic therapeutic approach and a possibility of prediction of IS-5-MN effects in different patient subsets.

This trial confirmed low-dose intravenous IS-5-MN as efficacious and safe for the treatment of patients with and without acute heart failure, in hemodynamic subsets I to IV, during acute myocardial infarction with significant symptomatic and hemodynamic effects and with no

appearance of nitrate tolerance over a period of 9.0 hours of continuous therapy. This efficacy seems to be partly prolonged over 3.0 to 4.0 hours because of IS-5-MN elimination half-life. Intravenous IS-5-MN, with its beneficial hemodynamic effects, stability of action and important safety profile, is an important addition to the spectrum of nitrates indicated for the therapy of acute heart failure during acute myocardial infarction.

REFERENCES

1. Flaherty JT. Role of nitrates in acute myocardial infarction. *Eur Heart J 1988;9:suppl A:165–170.*

2. Jugdutt BI, Warnica JW. Intravenous nitroglycerin therapy to limit myocardial infarct size, expansion and complications. *Circulation 1988;78:906–919.*

3. Bussmann WD, Schöfer H, Kaltenbach M. Wirkung von Nitroglycerin beim akuten Myokardinfarkt. II. Intravenöse Dauerinfusion von Nitroglycerin bei Patienten mit und ohne Linksinsuffizienz und ihre Auswirkungen auf die Infarktgrösse. *Dtsch. Med Wochenschr 1976;101:642–648.*

4. Rezaković D, Rutishauser W, Bloch A, Popadić M. Different hemodynamic actions of trinitroglycerin and isosorbid-dinitrate in patients with acute myocardial infarction. *Eur Heart J 1983;4:718–723.*

5. Rezaković D, Goldner V, Batinić Z, Štalec J, Pavičić L. Hemodynamic mechanisms of intravenous nitrates (NTG, ISDN and 5-ISM) in patients with different hemodynamic subsets during acute myocardial infarction. First International Symposium on Heart Failure, May 21–25. *1989 Jerusalem. Abstract No. 119.*

6. Barret RJ, McConnell WR, Melikian AP, Pierson WC, Abshagen UWP. Isosorbide-5-mononitrate. *Cardiovasc Drugs Rev 1988;6:54–70.*

7. Distante A, Lombardi M, Moscarelli E, Morales MA, L'Abbate A. Oral isosorbide-5-mononitrate can protect from myocardial ischemia induced by ergonovine test and by isometric effort. Preliminary results from an echocardiographic acute study in anginal patients. *Cardiology 1987;74:suppl 1:46–52.*

8. Arnim von Th, Erath A. Nitrates and calcium antagonists for silent myocardial ischemia. *Am J Cardiol 1988;61:15E–18E.*

9. Jansen W, Meyer L, Tauchert M. Acute effect of various doses of isosorbide-5-mononitrate on hemodynamic and exercise performance in coronary artery disease. *Am J Cardiol 1988;61:31E–35E.*

10. World Health Organization. Task force on standardization of clinical nomenclature: nomenclature and criteria for diagnosis of ischemic heart disease. *Circulation 1979;59:607–609.*

11. Forrester JS, Diamond GA, Chatterjee K, Swan HJC. Medical therapy of acute myocardial infarction by application of hemodynamic subsets. *N Engl J Med 1976;295:1356–1413.*

12. Cooley WW, Lohnes PR. Multivariate Data Analysis. *New York: John Wiley & Sons, 1971.*

13. Zakrajšek E, Štalec J, Momirović K. SS-program system for multivariate analysis of data. Proceedings of International symposium Computer on University. *Zagreb 1973;C8:1–16.*

14. Gammage MD, Murray RG, Littler WA. Isosorbide-5-mononitrate in the treatment of acute left ventricular failure following acute myocardial infarction. *Eur J Clin Pharmacol 1986;29:639–643.*

15. Rabinowitz B, Katz A, Shotan A, Chouraqui P, Neufeld HN. Haemodynamic effects of intravenous isosorbide-5-mononitrate in acute and chronic left heart failure of ischaemic aetiology. *Eur Heart J 1988;9:suppl A:175–180.*

16. Harf C, Welter R. Emergency treatment of severe cardiogenic pulmonary edema with intravenous isosorbide-5-mononitrate. *Am J Cardiol 1988;61:22E–27E.*

17. Lehmann HU, Polensky A. Hemodynamic effects of isosorbide-5-mononitrate in acute myocardial infarction. *Vascular Med 1984;October–December:195–204.*

18. Schneeweiss A. Comparative evaluation of isosorbide-5-mononitrate and nitroglycerin in chronic congestive heart failure. *Am J Cardiol 1988;61:19E–21E.*

19. Hutton I, McGhie AI, Martin W, Tweddel AC. A comparison of intravenous elantan and frusemide in patients with chronic heart failure. *Cardiology 1987;74:suppl 1:65–68.*

The American Journal of Cardiology

JUNE 19, 1990

A Symposium: International Update — The Important Role of Aldosterone and Aldosterone Antagonism in Cardiovascular Medicine

GUEST EDITOR:
David P. Lauler, MD
Clinical Associate Professor of Medicine
Yale University School of Medicine
New Haven, Connecticut
Chairman, Department of Medicine
Director of Medical Education
Lawrence and Memorial Hospital
New London, Connecticut

A YORKE MEDICAL JOURNAL/CAHNERS PUBLISHING COMPANY

The American Journal of Cardiology

JUNE 19, 1990 VOL. 65 NO. 23

A Symposium: International Update — The Important Role of Aldosterone and Aldosterone Antagonism in Cardiovascular Medicine

GUEST EDITOR:

David P. Lauler, MD

Clinical Associate Professor of Medicine
Yale University School of Medicine
New Haven, Connecticut
Chairman, Department of Medicine
Director of Medical Education
Lawrence and Memorial Hospital
New London, Connecticut

This supplement is based on symposia held in Brussels, Belgium, and Newport Beach, California, and was sponsored by G.D. Searle & Co.

EDITOR IN CHIEF
William C. Roberts, MD

MANAGING EDITOR, SPECIAL PROJECTS
Judith Wagner

PUBLISHER, SPECIAL PROJECTS
Kenton T. Finch

PRODUCTION EDITOR
Joan Gunning

PROOF EDITOR
Mary Crowell

THE AMERICAN JOURNAL OF CARDIOLOGY.® (ISSN 0002-9149) June 19, 1990, Vol. 65, No. 23 (USPS: 505–750).

Member, American Business Press, Inc. and Audit Bureau of Circulations. Published 4 times in January, February, March, May, June, July, September and October, 3 times in April, August and November, and 2 times in December, by The Cahners Publishing Company, a Division of Reed Publishing USA, 275 Washington St., Newton, MA 02158-1630. Terrence M. McDermott, President; Jerry D. Neth, Vice President/Publishing Operations; J.J. Walsh, Financial Vice President/Magazine Division; Thomas J. Dellamaria, Vice President/Production and Manufacturing.

SUBSCRIPTIONS: Solicited only from cardiologists and other physicians. Publisher reserves the right to refuse unqualified subscribers. Subscribers agree that no article or any part thereof published in any editions of the American Journal of Cardiology received under this subscription agreement may be copied, recorded or reproduced in any form or by any means, electronic or mechanical, including, among other things, photocopying or the storing of part or all of such articles on any information retrieval system, without the written permission of the Publisher. Address correspondence regarding subscriptions and changes of address to: THE AMERICAN JOURNAL OF CARDIOLOGY, 44 Cook Street, Denver, Colorado 80206-5800 (1-800-637-6073). Please include your zip code and, in case of change of address, copy of old address label. Changes of address must reach the Journal one month preceding month of issue. Single copy price: Regular issues $10.00; Symposium and special issues $12.00. Subscription rate for individuals in field of publication: United States 1 year $66, 2 years $112, 3 years $158; Canada and all other countries 1 year $105, 2 years $178, 3 years $252; Residents and Medical Students: United States 1 year $33; Canada & all other countries 1 year $85. Institutions: United States 1 year $95, 2 years $162, 3 years $228; Canada & all other countries 1 year $125, 2 years $213, 3 years $300. Air Mail available at additional charge of $150 per year. The Journal is not responsible for replacing missing issues unless the Circulation Department is notified of nonreceipt within 3 months of issue date.

Second class postage paid at Denver, CO, and at additional mailing office. Printed in U.S.A. Trademark™ in U.S. Patent Office. © Copyright 1990 by Reed Publishing USA: Saul Goldweitz, Chairman; Ronald G. Segel, President and Chief Executive Officer. All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording or by any information storage retrieval system, without permission of the copyright owner. Prices on bulk reprints of articles available on request.

The Publisher assumes no liability for any material published in the Journal. All statements are the responsibility of the authors.

MANUSCRIPTS: Address all manuscripts to William C. Roberts, MD, Editor-in-Chief, the American Journal of Cardiology, 7960 Old Georgetown Road, Suite 2C, Bethesda, Maryland 20814.

POSTMASTER: Send address changes to: The American Journal of Cardiology, 44 Cook Street, Denver, Colorado 80206-5800.

Cahners Publishing Company, A Division of Reed Publishing USA □ Specialized Business Magazines for Building & Construction □ Manufacturing □ Foodservice & Lodging □ Electronics & Computers □ Interior Design □ Printing □ Publishing □ Industrial Research & Technology □ Health Care □ Entertainment.

CABQUT CENTRAL LIBRARY

Publisher's Note

The opinions expressed in this presentation are those of the panelists and are not attributable to the sponsor or the publisher, editor, or editorial board of The American Journal of Cardiology. Clinical judgment must guide each physician in weighing the benefits of treatment against the risk of toxicity. References made in the articles may indicate uses of drugs at dosages, for periods of time, and in combinations not included in the current prescribing information.

Editor's suggestion: The symposium issues for a full year should be bound together separately from the regular issues.

CONTENTS

The American Journal of Cardiology

JUNE 19, 1990 VOL. 65 NO. 23

A SYMPOSIUM: INTERNATIONAL UPDATE — THE IMPORTANT ROLE OF ALDOSTERONE AND ALDOSTERONE ANTAGONISM IN CARDIOVASCULAR MEDICINE

1K
Introduction: Aldosterone and Spironolactone Revisited
David P. Lauler

Part I — Peripheral Action of Aldosterone and Aldosterone Antagonists

3K
Editorial Overview Denis L. Clement

4K
Aldactazine/Captopril Combination, Safe and Effective in Mild to Moderate Systemic Hypertension: Report on a Multicenter Study of 967 Patients Dominique C. Schohn, René Spiesser, Marie Wehrlen, Bruno Pelletier, and Michel-Hubert Capron

7K
Calcium-Channel Antagonist Effects of Spironolactone, an Aldosterone Antagonist Jean Mironneau

9K
Peripheral Action of Spironolactone: Arterial Elasticity
Gilbert Lagrue, Jean-Claude Ansquer, and André Meyer-Heine

12K
Peripheral Action of Spironolactone: Plethysmographic Studies Denis L. Clement

14K
Effects of a Potassium-Sparing/Thiazide Diuretic Combination on Cardiovascular Reactivity to Vasopressor Agents
Dominique C. Schohn and Henri A. Jahn

Part II — Antihypertensive Action of Spironoloactone and the Combination of Spironolactone and Altizide

18K
Editorial Overview: European Experience with Spironolactone and Thiazide Diuretic as Antihypertensive Therapy
David P. Lauler

20K
Clinical Update: Spironolactone and Altizide as Monotherapy in Systemic Hypertension Jean-Marc Dueymes

24K
Spironolactone and Altizide in Systemic Hypertension: Ambulatory Multicenter Study Jacques Sternon

28K
Spironolactone and Altizide Versus Converting Enzyme Inhibitor (Enalapril) Jean-Pierre Grünfeld, Marie Wehrlen, Bruno Pelletier, and Michel-Hubert Capron

33K
Spironolactone and Altizide Used in Combination with Enalapril: Twenty-Four-Hour Ambulatory Recording of Blood Pressure Pascal Poncelet, Marie Wehrlen, Bruno Pelletier, and Michel-Hubert Capron

36K
Spironolactone Versus Nifedipine in Essential Hypertension Michel Henry, Marie Wehrlen, Bruno Pelletier, and Michel-Hubert Capron

Part III — Considerations of Aldosterone in Congestive Heart Failure, Arrhythmias and Sudden Cardiac Death

39K
Editorial Overview Alain Castaigne

41K
Short- and Long-Term Mechanisms of Sudden Cardiac Death in Congestive Heart Failure Richard H. Helfant

44K
Relation of Cardiovascular Disease to Potassium and Magnesium Deficiencies Thomas Dyckner

47K
Role of Magnesium in Cardiac Tachyarrhythmias Lloyd T. Iseri

51K
Spironolactone in the Management of Congestive Heart Failure James E. Muller

54K
"Silent" Heart Failure as Observed by a French Cardiologist Alain Castaigne

The American Journal of Cardiology

Introduction: Aldosterone and Spironolactone Revisited

David P. Lauler, MD

Over 3 decades ago, Jerome Conn (University of Michigan) presented his clinical research findings on a patient with hypertension and hypokalemia. I doubt that few attending this presentation at a midwestern clinical research meeting appreciated the extraordinary drama unfolding. This was the original description of what is now called Conn's Syndrome, that is, primary aldosteronism due to an adrenal adenoma.[1] Conn's insight and diligence in the application of the physiology of aldosterone to his patient's problems provided one of the most memorable clinical success stories. The year was 1955. At that same time, major centers, including those of Luetscher et al[2] and Muller et al,[3] were expanding and delineating the knowledge of aldosterone, sodium and the genesis of edema disorders. It had been appreciated from the developing science of renal physiology that potent sodium-retaining hormones must be causing the excess of sodium retention in edema disorders, such as congestive heart failure and cirrhosis with ascites. Other investigators such as Davis et al[4] and Bartter[5] were quickly outlining control systems for the regulation of aldosterone secretion; clinicians such as Genest et al,[6] Biglieri et al,[7] and Spark and Melby[8] began the precise delineation of the biochemical clinical features in patients with aldosterone excess.

In retrospect, it was fortunate that a research pharmaceutical chemist working in Skokie, Illinois, developed a specific competitive antagonist to aldosterone in 1957.[9] This meant that from almost the initial application of this new knowledge regarding aldosterone, clinicians had a therapeutic tool available whereby they could antagonize the actions of the hormone, thereby judging the role the hormone played in a given clinical disorder.[10] The structural formula for spironolactone bears a striking similarity to the hormone aldosterone (Fig. 1). Spironolactone is a specific competitive antagonist acting at the cellular level where it preempts aldosterone molecules from binding with specific receptor sites, thereby diminishing the biologic activity of the aldosterone molecules.

Aldosterone receptors are thought to be distributed throughout the body wherever sodium is transported—kidneys, intestines, myocardium, blood vessels, skin and the brain. The utilization of this specific antagonist of aldosterone in treating patients with primary aldosteronism provided the crucial clinical experiment for the emerging role of aldosterone in hypertensive disorders.

When spironolactone, in higher (400 mg/day) than customary doses, is administered to patients with primary aldosteronism due to an adrenal adenoma, it results in a remarkable normalization of blood pressure, normalization of blood potassium and magnesium levels, and a decrease in the urine wasting of potassium and magnesium. That practicing physicians could control the biochemical abnormalities of aldosteronism, utilizing medical rather than surgical therapy, was most astonishing. From such considerations, it became readily evident that



David P. Lauler, MD

From the Yale University School of Medicine, New Haven, Connecticut.

Address for reprints: David P. Lauler, MD, Lawrence and Memorial Hospital, Montauk Avenue, New London, Connecticut 06320.

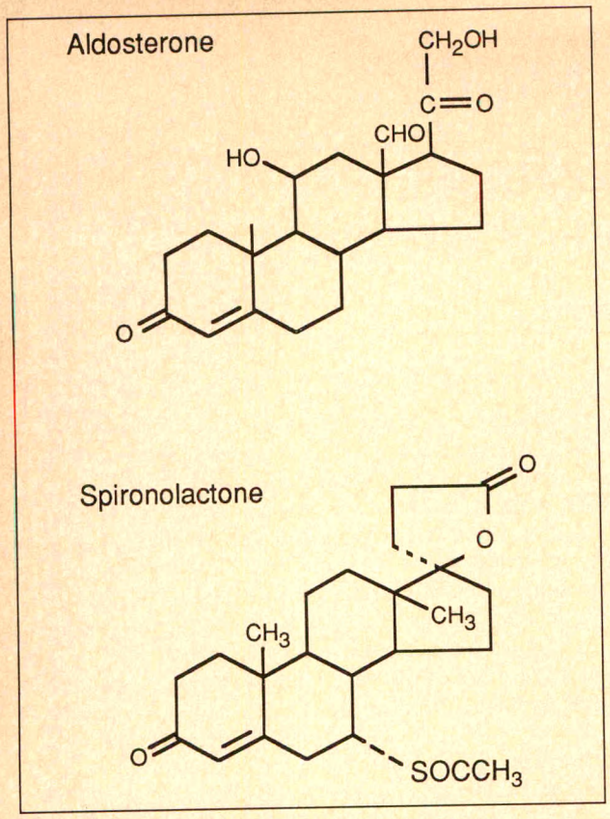


FIGURE 1. The structural formula for spironolactone.

the major role of aldosterone was to regulate extracellular fluid volume by enhancing tubular reabsorption of sodium in the distal nephron.

Under conditions of excess aldosterone there is a characteristic urine wasting of potassium and magnesium and simultaneous hypokalemia and hypomagnesemia. With the advent of reliable measurements of renin and angiotensin, it was appreciated that the renin-angiotensin system was the major control system for regulation of extracellular fluid volume via aldosterone. Equally important, parallel control systems for regulation of aldosterone involving adrenocorticotropic hormone and potassium were also identified. The importance of aldosterone in the overall homeostasis of the body can be appreciated, since no less than 3 parallel control systems are continuously operative.

Although it has always been evident that excess aldosterone could cause sodium retention and edema disorders, the relation between aldosterone activity and blood pressure levels has not been as straightforward. It is known that patients with primary aldosteronism can have sustained hypertension, which is relieved either by the administration of the specific aldosterone antagonist spironolactone, or which can be permanently relieved by the removal of the adrenal aldosterone-producing tumor. It has been postulated that hypertension in such patients is due to an enhanced vascular reactivity to aldosterone, related in some manner to sodium/calcium coupling of vasoactivity. Spironolactone, characteristically, is a mild antihypertensive but is potentiated by any of the commonly used diuretics.

With the increasing popularity of spironolactone as the ultimate potassium-regulating therapeutic agent, newer potassium-retaining agents became available (triamterene and amiloride). However, these newer agents are not aldosterone antagonists but cause potassium retention by direct effect on the renal tubules independent of aldosterone levels. This can prove to have an unwanted effect as there may be a stepwise increase in potassium retention leading to hyperkalemia. In contrast, spironolactone requires the presence of aldosterone to exert its characteristic potassium-retaining action. In the absence of aldosterone, potassium is not retained, thus providing a safety buffer to minimize problems of excessive potassium retention.

In the ensuing 3 decades since Conn's original observation, there has been explosive growth in the knowledge surrounding aldosterone and its application to specific clinical disorders. This particular journal supplement covers a wide array of therapeutic uses of spironolactone at widely ranging doses and in multiple combinations with other cardiovascular agents. The diversity of use of the aldosterone antagonist spironolactone is remarkable.

Despite the advent of major new therapeutic classes such as the β blockers, calcium channel blockers, and converting enzyme inhibitors, a well-defined role for the use of spironolactone continues to exist.

REFERENCES

1. Conn JW. Primary aldosteronism, a new clinical syndrome. *J Lab Clin Med 1955;45:3–17.*

2. Luetscher JA Jr, Johnson BB, Dowdy AJ, Hanery J, Lew W, Poo LJ. Observations of the sodium-retaining corticoid (aldosterone) in the urine of children and adults in relation to sodium balance and edema. *J Clin Invest 1954;3:1441–1446.*

3. Muller AF, Riondel AM, Manning EL, Mach RS. Study of aldosteronuria in normal subjects and oedematous disorders. *Schweiz Med Wochschr 1956;86: 1335–1339.*

4. Davis JO, Pechet MM, Ball WC Jr, Goodkind MJ. Increased aldosterone secretion in dogs with right-sided congestive heart failure and in dogs with thoracic inferior vena cava constriction. *J Clin Invest 1957;36:689–694.*

5. Bartter FC. Cardiac failure and hormonal control of fluid and electrolyte balance. *Surg Gynecol Obstet 1964;118:767–777.*

6. de Champlain J, Genest J, Veyrat R, le Boucher R. Factors controlling renin in man. *Trans Assoc Am Physicians 1965;78:135–157.*

7. Hunt TK, Schambelan M, Biglieri EG. Selection of patients and operative approach in primary aldosteronism. *Ann Surg 1975;182:353–361.*

8. Spark RF, Melby JC. Hypertension and low plasma renin activity: presumptive evidence for mineralocorticoid excess. *Ann Intern Med 1971;75:831–836.*

9. Kagawa CM, Cella JM, van Arman CG. Action of new steroids in blocking effects of aldosterone and desoxycorticosterone on salt. *Science 1957;126:1015–1016.*

10. Liddle GW. Specific and nonspecific inhibition of mineralocorticoid activity. *Metabolism 1961;10:1021–1030.*

Editorial Overview

Denis L. Clement, MD, PhD

Although the potassium- and magnesium-sparing diuretic spironolactone has been known and used for many years, aspects of its mechanism of action are still being discovered.

It has a large impact on hemodynamics, and there is a great deal of evidence to suggest that the antihypertensive activity of spironolactone is due, at least in part, to its vasodilator activity. For example, this effect is investigated in the article describing plethysmographic studies of the arterioles I performed with my colleagues. Lagrue demonstrates this vasodilator action of spironolactone in terms of its effect on the arterial elasticity of middle-sized arteries.

The mechanism of this vasodilation is investigated in 2 other papers. One, by Mironneau, shows that spironolactone has calcium-channel antagonist effects, which may explain in part the potency of the drug.

Schohn, looking at another aspect of spironolactone's antihypertensive mechanism of action, namely, its effect on cardiovascular reactivity, found that the vascular effect and the diuretic effect are quite distinct.

Finally, a large-scale multicenter study using spironolactone in combination with a thiazide diuretic provides the proved effectiveness of a diuretic with one of the new classes of drugs in patients in whom combination therapy is beneficial.

From University Hospital, Department of Cardiovascular Diseases, Gent, Belgium.

Address for reprints: Denis L. Clement, MD, PhD, University Hospital, Department of Cardiovascular Diseases, De Pintelaan 185, 9000 Gent, Belgium.

Aldactazine/Captopril Combination, Safe and Effective in Mild to Moderate Systemic Hypertension: Report on a Multicenter Study of 967 Patients

Dominique C. Schohn, MD, René Spiesser, MD,* Marie Wehrlen, MD, Bruno Pelletier, MD, and Michel-Hubert Capron, MD

The safety and efficacy of a thiazide/potassium-sparing diuretic and an angiotensin-converting enzyme inhibitor used concomitantly was evaluated in a large, multicenter study. Aldactazine® was administered alone for 2 months, after which time captopril was added in those whose blood pressure had not normalized (332 patients). At the end of the 6-month study, control of blood pressure was achieved in 88% of the patients with one or the other regimen. No clinically significant changes were recorded for a number of biologic parameters. Specifically, there was 1 case of hyperkalemia (6 mmol/liter), a very low incidence of hypotension (1.6%), and a low rate of adverse effects. Therefore, such a combination could provide important therapeutic benefits in hypertensive patients.

(Am J Cardiol 1990;65:4K–6K)

From the University Hospital, Strasbourg, Nephrology Department, CHR-Angers, and Laboratories Searle, Boulogne-Billancourt, France.

Address for reprints: Bruno Pelletier, MD, Laboratories Searle, 52 rue Marcel Dassault, 92514 Boulogne-Billancourt, France.

*Deceased.

Diuretics, especially thiazides, are generally used as first-line treatment of hypertension; however, such agents have been linked with cardiac arrhythmias caused by potassium and magnesium losses.[1] Aldactazine®, a drug that combines spironolactone and altizide, effectively reduces blood pressure, while sparing both potassium and magnesium. Captopril, an angiotensin-converting enzyme (ACE) inhibitor, is also effective in mild hypertension[2] and increases potassium balance, which is inversely related to glomerular filtration (creatinine clearance).[3] Because such agents are sometimes needed to supplement diuretics, the idea of a thiazide/potassium-sparing agent combination and an ACE inhibitor has raised some concern about the potential for hyperkalemia and renal insufficiency.[4] In addition, there have been reports of hypotensive accidents with enalapril in patients previously treated with diuretics.[5]

To evaluate the concomitant use of Aldactazine and an ACE inhibitor, we decided to conduct a large-scale study to determine both the efficacy and the safety of the Aldactazine/captopril combination.

METHODS

Patients: The investigators in this multicenter study, which involved 967 patients, were 200 family practitioners, since they are usually the initial prescribers of antihypertensive therapy.

The patients enrolled in the study had mild to moderate essential hypertension, either untreated or poorly controlled with previous therapeutic regimens. Blood pressure was measured in the supine position after 5 minutes' rest. Mild to moderate hypertension was defined as diastolic blood pressure between 100 and 120 mm Hg (Table I).

Therapy: After discontinuing any previous antihypertensive therapy, all patients were treated with 1 Aldactazine tablet (25 mg spironolactone, 15 mg altizide) daily for 2 months. The patients were not given a sodium-restricted diet. After 2 months, captopril (50 mg) was added to the regimen of those patients whose blood pressure had not normalized (diastolic blood pressure >95 mm Hg). The study was then continued for another 4 months.

Study parameters: The patients were seen at 8 weeks (2 months), 9 weeks, and 3, 4 and 6 months. At these

TABLE I Inclusion Criteria

Sex	Age (yr)	Diastolic Blood Pressure (mm Hg)	Potassium (mmol/liter)	Serum Sodium (mmol/liter)	Creatinine (μmol/liter)
M or F	18–75	100–120	3.5–5	135–145	<130

visits, weight, heart rate and blood pressure (standing and supine) were recorded. Other biologic parameters that were measured included urine protein, serum potassium, sodium, creatinine, cholesterol, uric acid and triglyceride levels. At the time of the 2-month visit, captopril was added to Aldactazine in those patients whose blood pressure was insufficiently controlled.

Statistical analysis: We used the chi-square test for the qualitative parameters and the Student-Fisher test for the quantitative parameters. These were applied to the patient population data and the safety and efficacy parameters.

ALDACTAZINE AND ALDACTAZINE/CAPTOPRIL ARE EFFECTIVE IN REDUCING BLOOD PRESSURE

After 2 months of monotherapy with Aldactazine, blood pressure was normalized in 635 of the 967 patients. Captopril was added to the regimen in the remaining 332 patients. The 2 population groups are not similar (Table II). One group was normalized with monotherapy, while the other needed the adjuvant therapy. It is apparent from the table that the patients who needed captopril tended to be men with a higher body weight, who had been hypertensive for a longer period, and who had received previous antihypertensive therapy.

Most patients' blood pressure was normalized with Aldactazine: At 2 months, blood pressure was controlled in 66% of the patients (635 of 967). Mean reduction in blood pressure (supine) was 18 mm Hg systolic and 14 mm Hg diastolic (Fig. 1).

Aldactazine + captopril controlled blood pressure in almost 90% of the patients: Ater 4 months of treatment, the combination treatment normalized blood pressure in 282 of the remaining 332 patients (84%). Systolic blood pressure (supine) was reduced by 22 mm Hg, and diastolic blood pressure by 19 mm Hg (Fig. 1). Overall, blood pressure was controlled in 88% (851 of 967) of the patients in the study.

RESULTS

Both Aldactazine and Aldactazine + captopril safely reduced blood pressure: There were no clinically significant changes in biologic parameters (Table III). In the Aldactazine group, body weight and heart rate remained essentially the same. Serum potassium did not vary greatly (slight reduction), and the increases in serum creatinine and uric acid were slight. No significant changes in serum sodium, cholesterol or triglycerides were recorded.

In the group treated with Aldactazine + captopril, body weight and heart rate were unchanged, as were serum creatinine, sodium, uric acid, cholesterol and triglycerides. Serum potassium decreased slightly (Table III).

TABLE II Demographic Characteristics

Patient Demographics	Group 1– Aldactazine	Group 2– Aldactazine + Captopril	Significance
Sex distribution* M/F	232/401 (36.5%/63.1%)	155/174 (46.7%/52.4%)	p = 0.001
Age (yr)	58.3 ± 11.3	58.1 ± 11.2	p = 0.88
Weight (kg)	72.6 ± 13.1	76.8 ± 14.6	p < 0.001
Family history of hypertension	251 (39.5%)	140 (42.2%)	p = 0.40
No previous antihypertensive therapy	389 (61.3%)	151 (45.5%)	p ≤ 0.001
Duration of hypertension (yr)	3.3 ± 4.4	5.0 ± 4.9	p < 0.001

* Does not include 2 patients from group 1 and 3 from group 2.

One week after initiation of treatment, the difference between supine and standing systolic blood pressure was ≥20 mm Hg (risk of orthostatic hypotension) in 1.6% of the patients.

Adverse effects were few and minor: Muscle cramps were reported by the patients in the Aldactazine group (1.6%). In the combination group, digestive disturbances (4.8%), dizziness (3%) and weakness (1.5%) were reported.

CONCLUSIONS

Aldactazine/captopril combination is both safe and effective: This study was conducted to evaluate whether a thiazide/potassium-sparing diuretic and an ACE inhibi-

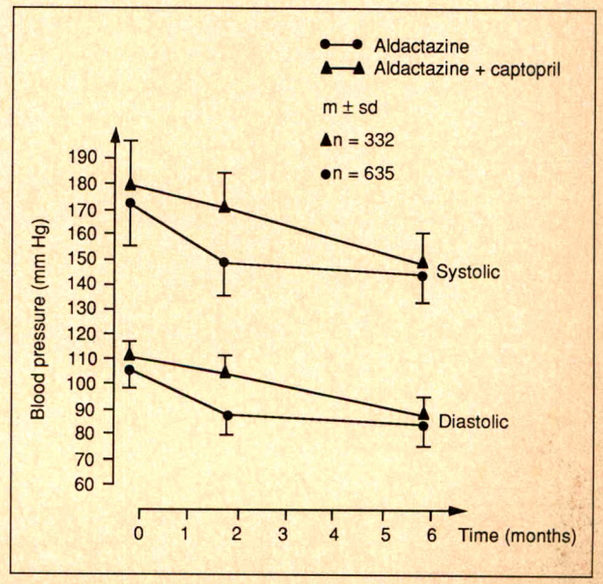


FIGURE 1. Changes in supine blood pressure after treatment with Aldactazine alone or with Aldactazine + captopril. m + sd = mean ± standard deviation.

TABLE III Biologic Parameters

Parameter	Status	Aldactazine Group	p	Aldactazine + Captopril	p
Weight (kg)	Before treatment	72.6 ± 13.1	<0.01	76.8 ± 14.6	<0.01
	After treatment	71.4 ± 12.8		75.5 ± 14.0	
Heart rate (beats/min)	Before treatment	77 ± 9	<0.01	80 ± 10	<0.01
	After treatment	76 ± 8		76 ± 8	
Serum potassium (mmol/liter)	Before treatment	4.26 ± 0.35	<0.01	4.30 ± 0.37	<0.01
	After treatment	4.18 ± 0.37		4.26 ± 0.37	
Serum sodium (mmol/liter)	Before treatment	139.9 ± 2.3	<0.01	140.0 ± 2.5	NS
	After treatment	139.5 ± 3.0		139.6 ± 3.0	
Serum creatinine (μmol/liter)	Before treatment	86 ± 17	<0.01	90 ± 17	NS
	After treatment	88 ± 16		92 ± 15	
Serum cholesterol (mmol/liter)	Before treatment	6.2 ± 1.3	<0.01	6.4 ± 1.2	<0.01
	After treatment	6.1 ± 1.2		6.2 ± 1.1	
Serum uric acid (μmol/liter)	Before treatment	325 ± 78	<0.01	341 ± 72	NS
	After treatment	336 ± 76		342 ± 72	
Triglycerides (mmol/liter)	Before treatment	1.6 ± 0.9	NS	1.8 ± 0.9	<0.05
	After treatment	1.6 ± 0.7		1.7 ± 0.7	

NS = not significant.

tor could be safely used together in the treatment of mild to moderate hypertension.

By the end of the study, blood pressure was well controlled in 88% of the patients. Specifically, the study showed that the danger for hyperkalemia was minimal. In addition, there was a very low rate of dizziness, which occurred early in the treatment phase. This combination proved to be safe in all other respects as well, with no clinically significant changes in important biologic parameters, such as patients' heart rate levels, creatinine, uric acid, cholesterol and triglyceride levels.

Data from this study suggest that practicing physicians should consider adding an ACE inhibitor to a thiazide/potassium-sparing diuretic combination, Aldactazine, to control hypertension. Not only will hypertension likely be controlled in most cases, but there should be minimal perturbation of electrolytes, provided that the patients have no renal insufficiency and do not have diabetes.

REFERENCES

1. Hollifield JW. Potassium and magnesium abnormalities: diuretics and arrhythmias in hypertension. *Am J Med 1984;77:28–32.*

2. Stumpe KO, Overlack A, Kolloch R, Schreyer S. Long-term efficacy of angiotensin-converting-enzyme inhibition with captopril in mild-to-moderate essential hypertension. *Br J Clin Pharmacol 1982;14:121S–126S.*

3. Textor SC, Bravo EL, Fouad FM, Tarazi RC. Hyperkalemia in azotemic patients during angiotensin-converting enzyme inhibition and aldosterone reduction with captopril. *Am J Med 1982;73:719–725.*

4. Hodsman GP, Johnston CI. Angiotensin converting enzyme inhibitors: drug interactions. *J Hypertens 1987;5:1–6.*

5. Webster J, Newnham DM, Petrie JC. Initial dose of enalapril in hypertension. *Br Med J 1985;290:1623–1624.*

Calcium Channel Antagonist Effects of Spironolactone, an Aldosterone Antagonist

Jean Mironneau, DSc

The effect of spironolactone on the contractility of vascular smooth muscle cells and on calcium channel currents of isolated cells was investigated using the patch-clamp method. Concentrations of 10 and 60 μM of spironolactone resulted in 50 and 100% inhibition, respectively, of isometric contractions. Whereas fast calcium channel current was essentially unaffected by spironolactone, slow calcium channel current was inhibited 50% by 5 to 7 μM concentrations of the drug. These results suggest that spironolactone acts on slow calcium channels in a manner similar to that of calcium blockers.

(Am J Cardiol 1990;65:7K–8K)

From the Cellular Physiology and Molecular Pharmacology Laboratory, Centre National de la Recherche Scientifique, Bordeaux, France.

Address for reprints: Jean Mironneau, DSc, Laboratoire de Physiologie Cellulaire et Pharmacologie Moléculaire, 3 Place de la Victoire, 33076-Bordeaux Cedex, France.

Spironolactone, a mineralocorticoid, competitively inhibits the effects of aldosterone in a number of mammalian tissues,[1] and has diuretic and antihypertensive properties comparable with those of thiazide diuretics. This aldosterone antagonist reduces blood pressure without any significant effect on plasma concentration of potassium ions. In addition, spironolactone has been found to have a positive inotropic effect and to increase amplitude and duration of the action potential in mammalian myocardial preparations.[2]

The goal of this study was to investigate potential calcium channel-blocking properties of spironolactone in vascular smooth muscle and, if such properties were demonstrated, to determine their mechanism of action.

INHIBITION OF CALCIUM CURRENT

The effects of spironolactone on isometric contractions (in polarized and depolarized preparations) as well as on the calcium current in the calcium channels of isolated cells of vascular smooth muscles were studied. The experiments were performed on sections of rat portal veins. Contractile activity was measured in an experimental chamber described previously.[3] The cells, isolated by the method described by Loirand et al,[4] were investigated using patch electrodes and the whole-cell clamp mode.[5] The solutions were prepared as described elsewhere.[6]

Fifty percent inhibition of isometric contractions of vascular smooth muscle was obtained with concentrations of 10 μM of spironolactone, 80 μM of hydrochlorothiazide and 400 μM of chlorthalidone. Total (100%) inhibition of isometric contractions was achieved with 60 μM of spironolactone (Table I).

At concentrations of 60 μM, spironolactone had no effect on fast calcium channel currents. However, slow calcium channel current was blocked in a dose-dependent manner. Spironolactone concentrations between 5 and 10 μM yielded 50% inhibition of slow calcium channel current.[6]

The increase in intracellular calcium concentration was responsible for the activation of contraction in the smooth muscle preparations. It has been suggested that there are 2 sources of intracellular ionized calcium: (1) an intracellular storage site (the sarcoplasmic reticulum),[7] and (2) an extracellular source through 2 types of voltage-dependent calcium channels.[4]

DISCUSSION

Types of calcium channels: There are 2 types of calcium channels, fast calcium channels, available at membrane potentials near −70 mV, and slow channels, at potentials near −40 mV.

TABLE I Inhibition of Vascular Contractility by Spironolactone, Hydrochlorothiazide and Chlorthalidone

	$IC_{50}(\mu m)$	$IC_{100}(\mu m)$
Spironolactone	10	60
Hydrochlorothiazide	80	—
Chlorthalidone	400	—

IC_{50} and IC_{100} are the concentrations producing half-maximal and complete inhibition.

The following conclusions may be drawn from the experiments noted before: (1) A 10 μM concentration of spironolactone produces a 50% inhibition of slow calcium channels. This concentration also inhibits muscular contractility by 50%. This is evidence that spironolactone has an effect on calcium channels. (2) The influx of calcium through the fast calcium channels was not significantly affected by spironolactone. This suggests that spironolactone acts only on the slow calcium channels.

Configurations of calcium channels: Calcium channels have 3 different configurations depending on the membrane potential (Fig. 1). (1) A "resting" state (R), with no calcium current (resting potential = −60 mV); (2) an "open" state (O), with an influx of calcium from outside the cell; and (3) an "inactivated" state (I), with no calcium current, but in which the configuration of the channels is different from their resting configuration.

The transition from R to O is called activation phase (≤1 ms). The transition from O to I is called inactivation phase (≥10 ms), and the transition from I to R is called recuperation phase (≥1 second) (Fig. 2).

Mechanism of spironolactone inhibition: When diphydropyridine derivatives are tested for their ability to block calcium channels, their effects are observed to depend on depolarized holding potentials rather than on the frequency or number of stimuli used to promote the calcium channel opening.[8] Accordingly, we have studied whether the action of spironolactone depends on the number of command pulses applied (use-dependence) or on depolarized holding potentials (voltage-dependence). These results indicate that spironolactone binds to all states of the slow calcium channels with a similar affinity.

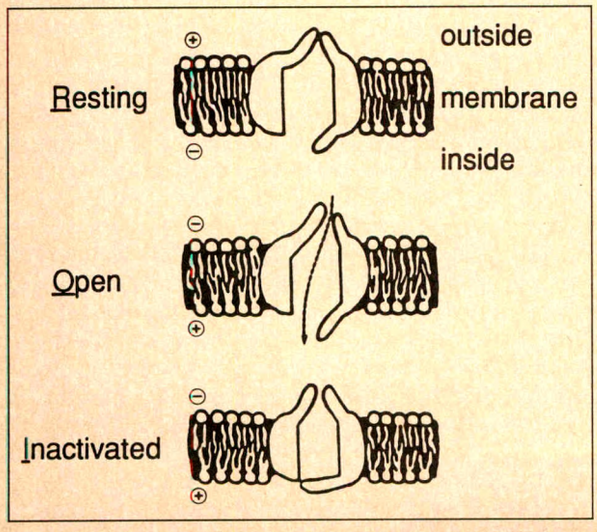


FIGURE 1. Configurations of calcium channels depending on the membrane potential.

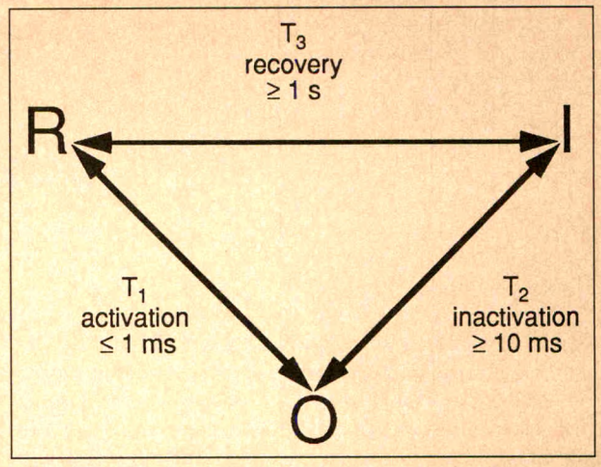


FIGURE 2. Calcium channels: Transitions from resting to open and inactivated state are regulated by the time constants at a given membrane potential. s = second.

Molecular effects: Spironolactone partially antagonizes the specific binding of 2 calcium channel blockers, (+)[^{3}H]-isradipine and (−)[^{3}H]desmethoxyverapamil, to vascular membranes. The IC_{50} values found in binding experiments are similar to the IC_{50} value for half-maximal inhibition of slow calcium channel current.

CONCLUSIONS

These results show that only spironolactone, at concentrations of 10 and 60 μM, was able to inhibit the slow calcium channels of smooth muscle cell membranes. Although spironolactone's effect on calcium channels appears to be different from that of calcium channel blockers, it may have a complementary effect.

REFERENCES

1. Ramsay LE. Clinical pharmacology and therapeutic use of aldosterone antagonists. In: Agarwal MK, ed. Hormone Antagonism. *Berlin: W De Gruyter, 1982:335–363.*

2. Coraboeuf E, Deroubaix E. Effect of a spironolactone derivative, sodium canrenoate, on mechanical and electrical activities of isolated rat myocardium. *J Pharmacol Exp Ther 1974;191:128–138.*

3. Mironneau J, Lalanne C, Mironneau C, Savineau JP, Lavie JI. Comparison of pinaverium bromide, manganese chloride and D600 effects on electrical and mechanical activities in rat uterine smooth muscle. *Eur J Pharmacol 1984;98:99–107.*

4. Loirand G. Pacaud P, Mironneau C, Mironneau J. Evidence for two distinct calcium channels in rat vascular smooth muscle cells in short-term primary culture. *Pflügers Arch 1986;407:566–568.*

5. Hamill OP, Marty A, Neher E, Sakmann E, Sigworth FJ. Improved patch-clamp techniques for high-resolution current recording from cells and cell-free membrane patches. *Pflügers Arch 1981;391:85–100.*

6. Dacquet C, Loirand G, Mironneau C, Mironneau J, Pacaud P. Spironolactone inhibition of contraction and calcium channels in rat portal vein. *Br J Pharmacol 1987;92:535–544.*

7. Nanjo T. Effects of noradrenaline and acetylcholine on electro-mechanical properties of the guinea pig portal vein. *Br J Pharmacol 1984;81:427–440.*

8. Dacquet C, Pacaud P, Loirand G, Mironneau C, Mironneau J. Comparison of binding affinities and calcium current inhibitory effects of a 1,4-dihydropyridine derivative (PN 200-110) in vascular smooth muscle. *Biochem Biophys Res Commun 1988;152:1165–1172.*

Peripheral Action of Spironolactone: Improvement in Arterial Elasticity

Gilbert Lagrue, MD, Jean-Claude Ansquer, MD, and André Meyer-Heine, MD

Arterial elasticity, which can be assessed by means of a piezogram, is thought to be involved in the development of hypertension. In hypertensive patients (and with aging in normal subjects), arterial elasticity is reduced. Long-term administration of spironolactone, β blockers, or a β-blocker/dihydralazine combination to hypertensive patients sufficiently reduced systolic and diastolic blood pressure to about the same extent; however, only spironolactone had any effect on piezoelectric indexes of arterial elasticity.

(Am J Cardiol 1990;65:9K–11K)

From the Department of Nephrology, Hôpital Henri Mondor, Créteil, France.

Address for reprints: Gilbert Lagrue, MD, Hôpital Henri Mondor, Boulevard de Lattre de Tassigny, 94010 Créteil, France.

In recent years, an increasingly important role has been attributed to arterial elasticity in the development of hypertension. Arterial elasticity (or distensibility) can be assessed by the velocity of the pressure wave along the arterial wall, which increases as elasticity decreases. This velocity can be calculated directly by measuring the amount of time for the wave to travel (transmission) between 2 points in the arterial system, e.g., from the carotid artery to the pedal artery or the carotid artery to the radial artery. This velocity is increased in hypertensive subjects, and it gradually increases with age, as a sign of arterial aging (Fig. 1, Table I).[1–5]

MEASURING ARTERIAL ELASTICITY

The carotid piezogram records waveforms of (arterial) blood pressure obtained noninvasively by means of a piezoelectric pressure gauge that translates pressure variations into variations of electric potential.

The curve is recorded on an oscilloscope, with a spot sectioned at 1/100th of a second. The waveform is the result of the intersection of 2 fundamental waves: the primary wave of ventricular pressure and a reflection wave (dicrotic wave). The peak of the curve corresponds to the systolic blood pressure and the trough corresponds to the diastolic blood pressure (Fig. 2). Also, the curve is characterized by various factors that regulate blood pressure, especially cardiac output (ventricular pressure) and peripheral resistance, of which arterial elasticity is a component.[3,4]

Velocity can also be determined indirectly by measuring the duration of the crest of the dicrotic wave, which is closely correlated with the transmission time ($r = 0.75$; $p < 0.001$). As arterial elasticity decreases, the velocity of the dicrotic wave increases, and the dicrotic wave appears sooner. The shorter the dicrotic wave, the greater the reduction in arterial elasticity.[1,4] In healthy subjects, the dicrotic wave shortens with age (Table II). In chronic hypertension, the systolic slope (AB) is increased and the dicrotic wave is shortened (Fig. 2).

We systematically studied variations in carotid piezogram values in hypertensive patients receiving long-term treatment with spironolactone ($n = 33$), β blockers ($n = 35$), and a combination β-blocker/dihydralazine ($n = 19$) (Table III). The piezogram and blood pressure values before and after treatment (>1 year) were compared. The decreases in systolic and diastolic blood pressure were similar for the 3 treatment groups (Table IV), although it was more marked with spironolactone and the β-blocker/dihydralazine combination than with β blockers alone.

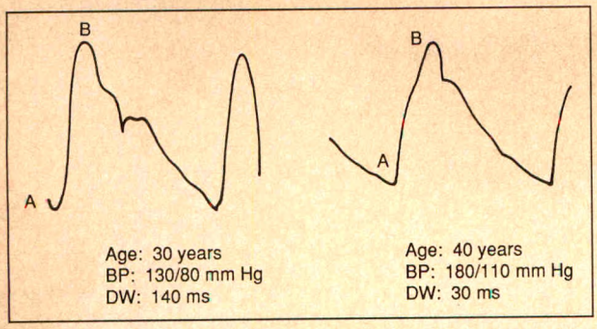


FIGURE 1. Carotid piezogram of a young healthy adult and an older hypertensive patient. AB = systolic slope; BP = blood pressure; DW = dicrotic wave.

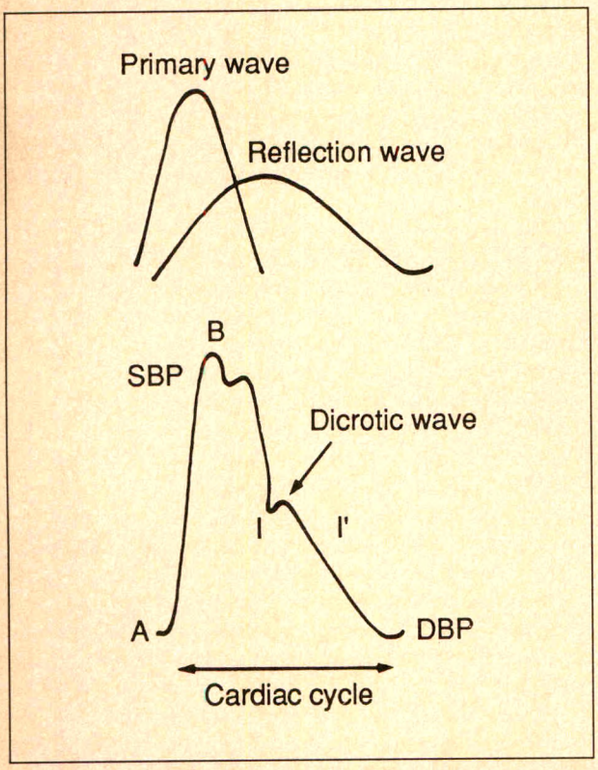


FIGURE 2. Carotid piezogram of a healthy young adult. AB = systolic slope; DBP = diastolic blood pressure; I I' = duration of dicrotic wave; SBP = systolic blood pressure.

However, the piezogram values were very different. With spironolactone, the dicrotic wave was significantly lengthened, indicating an improvement in arterial elasticity. This improvement was confirmed by an increase in the systolic slope. These changes were not found with either the β blockers (dicrotic wave moderately shortened) or with the β-blocker/dihydralazine combination (dicrotic wave and systolic slope unchanged) (Fig. 3 and 4, Table IV).

CONCLUSIONS

It is clear, therefore, that these different agents reduce blood pressure by different mechanisms. As seen here, spironolactone improves arterial elasticity, possibly by changing reactivity to pressor substances, which are

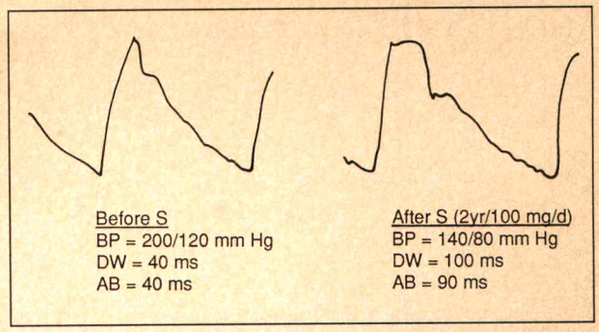


FIGURE 3. Carotid piezogram of a hypertensive patient before treatment and after 2 years of treatment with spironolactone(s). Abbreviations as in Figure 1.

TABLE I Changes in Piezogram Parameters with Increasing Age

Age (yr)	Transmission Time (ms)	Pressure Wave Velocity (ms)
<20	210	6.5
20–29	170	8
30–49	154–162	8.6–8.8
50–69	130	9.9–10.2
>70	110	>12

TABLE II Age-induced Changes in Crest of Dicrotic Wave (Carotid Piezogram)

Age (yr)	Crest of Dicrotic Wave (ms)
15–29	137 ± 41
30–49	87 ± 21
>50	50 ± 29

TABLE III Demographic Parameters of the Three Patient Groups

Spironolactone group, 100–200 mg/day (n = 33)	
Mean age	46 years (21–64)
Men/women	23/10
Mean duration of treatment	44 months (6–72)
Duration of hypertension	6.5 years (1–18)
Serum creatinine	9–13 mg/liter
β-blocker group (n = 35)	
Mean age	38 years (16–56)
β-blocker + dihydralazine group (n = 19)	
Mean age	46 years (30–61)
Chronic hypertension	>150/90 (at rest)

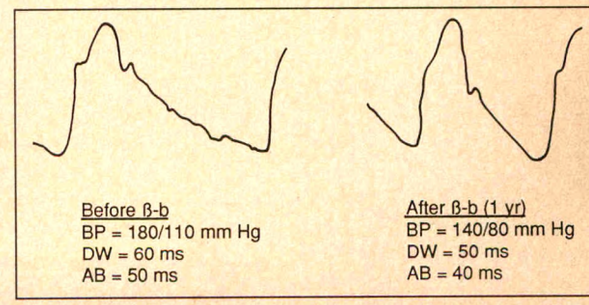


FIGURE 4. Carotid piezogram of a hypertensive patient before treatment and after 1 year of treatment with a β blocker (B-β). Abbreviations as in Figure 1.

TABLE IV Effect of Long-Term Administration of Spironolactone, β Blockers, or β Blocker + Dihydralazine on Blood Pressure and Carotid Piezogram Indexes of Arterial Elasticity (Dicrotic Wave and Systolic Slope)

	Systolic BP	Diastolic BP	Dicrotic Wave (ms)	AB Duration (ms)
Spironolactone				
Before	178 ± 28	100 ± 15	41.2 ± 29.6	44 ± 15
After	140 ± 15*	80 ± 8*	54.2 ± 34†	60 ± 16*
β blocker				
Before	164 ± 21	96 ± 12	61 ± 34	54 ± 1
After	149 ± 23†	87 ± 14†	51 ± 34	57 ± 19
β blocker + dihydralazine				
Before	171 ± 20	97 ± 15	51 ± 27	54 ± 22
After	144 ± 20†	82 ± 11*	51 ± 19	53 ± 18

* $p < 0.001$; † $p < 0.01$.
AB = systolic slope; BP = blood pressure.

known to play an important role in vascular distensibility. This favorable vascular effect could also be due to alteration of transmembrane sodium transport found with spironolactone.

REFERENCES

1. Kannel WB, Wolf PA, McGee DL, Dawbert T, McNamara P, Castelli WP. Systolic blood pressure, arterial rigidity and risk of stroke. *JAMA 1981;245:1224–1229.*

2. Lax M, Feinberg A, Cohen B. Studies of the arterial pulse wave. The normal pulse wave and its modification in the presence of arterial arteriosclerosis. *J Chronic Dis 1956;3:618–631.*

3. Merillon JP, Lebras Y, Chastre J, Gourgon G. Ondes incidentes and réfléchies dans le système artériel; application à l'interprétation quantitative de la morphologie de la pression aortique. *Arch Mal Coeur 1983;76:120–127.*

4. Meyer-Heine A, Ansquer J-C, Kazandjian M, Lagrue G. De l'analyse du carotidogramme au mécanisme de l'hypertension arterielle. *Sem Hôp Paris 1987;63:2663–2669.*

5. Simon AC, Levenson JA, Bouthier JD, Safar ME. Evidence of early degenerative changes in large arteries in human essential hypertension. *Hypertension*

Peripheral Action of Spironolactone: Plethysmographic Studies

Denis L. Clement, MD, PhD

The relation between vasodilation and the blood pressure–reducing action of spironolactone was studied in a randomized, placebo-controlled, double-blind, crossover study using 9 patients with essential hypertension. Vasodilation was studied by measuring blood flow in finger and calf (representative of skin and muscle circulation) by an electrocardiographic-triggered venous-occlusion plethysmograph. Treatment with spironolactone (100 mg twice daily for 4 weeks) produced significant decreases in systolic and diastolic blood pressure without significantly affecting heart rate. Blood flow through finger and calf increased, sometimes markedly, in 6 of the 9 patients, while vascular resistance decreased. This study confirms that the antihypertensive action of spironolactone is associated with vasodilation in many patients.

(Am J Cardiol 1990;65:12K–13K)

From the Department of Cardiovascular Diseases, University of Gent, Belgium.

Address for reprints: Denis L. Clement, MD, PhD, University Hospital, Department of Cardiovascular Diseases, De Pintelaan 185, 9000 Gent, Belgium.

Although spironolactone has been used for many years to treat hypertension, little is known about its hemodynamic action. Some investigators have shown that the antihypertensive effect of spironolactone is caused by dilation of the resistance vessels.[1] Other investigators report that spironolactone's hypotensive action results from a decrease in cardiac output or total peripheral resistance, or both.[2] In these studies, however, the vascular effect was determined indirectly by calculating total peripheral vascular resistance (blood pressure divided by cardiac output). Because blood vessels do not always respond in the same fashion,[3,4] we decided to investigate the peripheral hemodynamic effect of spironolactone by direct measurement of blood flow.

METHODS

Study design: This study was an 8-week, double-blind, crossover comparison, involving 9 patients with moderate hypertension serving as their own controls. Four weeks before the beginning of the study, placebo was substituted for the antihypertensive drug. The drugs were placebo and spironolactone (100 mg given twice daily).

Baseline tests: Physical examination, including auscultation of renal arteries and palpation of femoral arteries, yielded no abnormal findings in any of the patients. In addition, the results of renal function tests and measurements of plasma sodium, potassium and 24-hour urine catecholamines were all within normal limits. Electrocardiographic and chest x-ray results were normal as well. Retinal changes observed were consistent with group 1 or 2 hypertension (Keith-Wagener-Barker classification).

Study tests: Blood pressure and heart rate (supine, sitting and standing) were determined. Blood flow in the finger and calf (representative of skin and muscle circulation)[4] was measured over a 20-minute period by an electrocardiographic-triggered venous-occlusion plethysmograph (Periflow,® Janssen), with simultaneous measurement of changes in volume by mercury-filled tubes placed around the calf and finger.

RESULTS

Blood pressure and heart rate: Compared with placebo, spironolactone significantly reduced blood pressure in patients in the supine, sitting and standing positions (Fig. 1).[5] After treatment with spironolactone, heart rates in the sitting and standing positions were slightly, but not significantly, increased (85 ± 4 vs 82 ± 4 beats/min with placebo, and 90 ± 5 vs 83 ± 4 beats/min with spironolactone, respectively).

TABLE I Effect of Placebo and Spironolactone on Blood Flow and Vascular Resistance

	Blood Flow (vol %/min)						Vascular Resistance (U/min)					
	Finger			Calf			Finger			Calf		
Pt	P	S	Change (%)	P	S	Change (%)	P	S	Change (%)	P	S	Change (%)
1	9.452	13.906	47.1	9.718	25.244	159.8	13.119	7.623	−41.9	12.760	4.199	−67.1
2	5.364	7.199	34.2	9.936	24.066	142.2	20.020	11.113	−44.5	16.735	3.324	−80.1
3	3.724	4.560	22.4	12.909	33.516	159.6	32.760	24.561	−25.0	9.451	3.342	−64.6
4	4.562	5.377	17.9	36.592	24.160	−34.0	35.217	23.063	−34.5	4.391	5.133	16.9
5	5.463	4.750	−13.0	3.018	9.814	225.2	20.380	21.582	5.9	36.895	10.530	−71.4
6	5.219	6.370	22.0	23.551	16.880	−28.3	28.100	20.310	−27.7	6.228	7.660	23.0
7	2.902	2.700	−7.0	6.253	14.121	125.8	42.953	36.790	−14.3	19.938	7.034	−64.7
8	3.701	3.800	2.7	7.819	12.667	62.0	30.802	26.667	−13.4	14.579	7.984	−45.2
9	8.871	3.830	−56.8	8.705	2.768	−68.2	14.504	28.028	93.2	14.782	38.783	162.4
Mean	5.473	5.832	6.6	13.167	18.137	37.8	26.428	22.193	−16.0	15.084	9.777	−35.2

P = placebo; S = spironolactone.

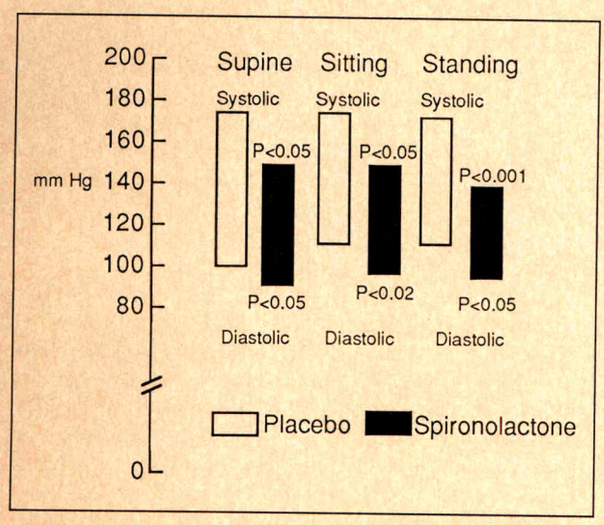


FIGURE 1. Effect of placebo and spironolactone (100 mg/day twice daily) on blood pressure in 9 hypertensive patients. Average decrease in blood pressure: supine—27 ± 9 mm Hg systolic and 10 ± 5 mm Hg diastolic ($p < 0.05$); sitting—27 ± 4 mm Hg systolic ($p < 0.001$) and 11 ± 4 mm Hg diastolic ($p < 0.02$); standing—36 ± 6 mm Hg systolic ($p < 0.001$) and 17 ± 4 mm Hg diastolic ($p < 0.005$). (Adapted from *Eur J Clin Pharmacol.*[5])

Blood flow (finger and calf vessels): In most cases, spironolactone induced vasodilation, i.e., blood flow in the finger and calf increased in 6 of 9 patients (Table I). This increase was quite large in some instances (up to 225% for calf flow). Conversely, vascular resistance decreased (up to 80%) in most patients, although 3 patients experienced an increase.

Adverse reactions: Two patients reported gastrointestinal disturbances, which resolved spontaneously. In 1 patient who complained of dizziness, the dosage was reduced to 100 mg/day for 1 week. The 100-mg dosage twice daily was resumed the following week.

DISCUSSION

As expected, treatment with spironolactone produced a significant decrease in the systolic and diastolic blood pressures. As shown by the decrease in vascular resistance and the increase in blood flow in the finger and calf in 6 of 9 patients, the blood pressure–reducing effect of spironolactone is accompanied by vasodilation. However, as noted by previous investigators,[2,6] other mechanisms are involved in the reduction of blood pressure, since vascular resistance was either unchanged or increased in 3 patients whose resistance was comparable to that of the other patients during the control period. The antihypertensive effect observed in these patients may possibly be attributed to a decrease in cardiac output or to dilation of vessels other than those studied here; however, because vasodilation was so marked in 6 patients, the evidence strongly suggests that it is directly linked to a decrease in blood pressure.

REFERENCES

1. Bevegård S. The effect of four months' treatment with spironolactone on systemic blood pressure, cardiac output and plasma renin activity in hypertensive patients. *Acta Med Scand 1977;202:373–377.*

2. Falch DK, Johansson R, Ødegaard AE, Norman N. Haemodynamic effects of treatment and withdrawal of spironolactone in essential hypertension. *Scand J Clin Lab Invest 1979;39:159–165.*

3. Clement DL, Shepherd JT. Regulation of peripheral circulation during muscular exercise. *Prog Cardiovasc Dis 1976;15:23–31.*

4. Shepherd JT, Vanhoutte PM. Neurohumoral regulation. In: Shepherd JT, Vanhoutte PM, eds. The Human Cardiovascular System. Facts and Concepts. *New York: Raven Press, 1980:107–155.*

5. Clement DL. Effect of spironolactone on systemic blood pressure, limb blood flow and response to sympathetic stimulation in hypertension patients. *Eur J Clin Pharmacol 1982;21:263–267.*

6. Safar ME. Vasodilators, a key point in hypertension. In: Safar ME, ed. *Stuttgart, New York: Schattauer, 1989:115–132.*

Effects of a Potassium-Sparing/Thiazide Diuretic Combination on Cardiovascular Reactivity to Vasopressor Agents

Dominique C. Schohn, MD, and Henri A. Jahn, MD

The vascular effects of a diuretic combination (spironolactone/altizide) were studied in 5 anuric patients undergoing dialysis by measuring changes in cardiovascular reactivity to norepinephrine (NE) and angiotensin II (AII) after infusion of incremental doses of these 2 vasopressor agents. There was a marked dose-response relation between NE and AII administration and mean (NE) or diastolic (AII) blood pressure (BP). Diuretic treatment moderated the increase in mean or diastolic BP induced by NE or AII. In addition, the pressor doses of NE and AII, which are also parameters of vascular reactivity, were significantly increased after diuretic treatment (NE, +101%; AII, +163%). Right atrial and pulmonary capillary wedge pressures increased along with BP in response to NE. Diuretic treatment also moderated the increase in right atrial and pulmonary capillary wedge pressures induced by NE. These results suggest that the antihypertensive action of spironolactone and altizide in combination is mainly due to a direct effect on resistance and capacitance vessels. The mechanisms by which diuretics modify the cardioreactivity remain poorly understood; however, they may modify electrolyte transport (sodium and calcium) across vascular smooth muscle cell membranes or stimulate postaglandin release.

(Am J Cardiol 1990;65:14K–17K)

From the Nephrology and Hemodialysis Department, Louis Pasteur University, Strasbourg, France.

Address for reprints: Dominique C. Schohn, MD, Service de Néphrologie et d'hémodialyse, CHR & U, 1, Place de l'Hôpital, 67085 Strasbourg-Cedex, France.

Despite the advent of new classes of antihypertensive agents, diuretics by and large have remained the therapy of first choice for the treatment of hypertension.[1] They have been used for more than 25 years and have proved to be effective in almost all forms of hypertension, whether used alone or in combination with other types of antihypertensives. However, how they exert their action has not been completely elucidated, especially as diuretics reduce blood pressure (BP) by way of a variety of mechanisms. A number of studies have shown that the antihypertensive effect of diuretics is not only a consequence of a negative water and sodium balance, but also the result of an unrelated vascular effect.[2] Whereas the diuretic effect is not apparent until fairly high doses are reached, the vascular effect is evident at low doses.[3] All diuretics, whether loop, thiazide or potassium sparing, have been shown to have specific vascular effects.[4–6] In a previous study, we demonstrated that the specific vascular effects of diuretics are mainly induced by changes in cardiovascular reactivity to norepinephrine (NE) and to angiotensin II (AII).[4] We conducted this study to explore the specific vascular effects of a combination diuretic consisting of a potassium-sparing diuretic (spironolactone) and a thiazide diuretic (altizide). To avoid the renal effects of the drug (from the potential effect of a negative sodium and water balance), the study was conducted in patients who undergo chronic hemodialysis.

METHODS

Five oliguric patients (4 men and 1 woman, mean age 53 ± 13 years), undergoing chronic hemodialysis on a regular hemodialysis program for at least 6 months, were studied. All were volunteers and all gave informed consent before the study. None of these patients presented with cardiac disease or diabetes, and the predialysis kalemia of these subjects was always within the normal range. No patient was receiving cardiovascular therapy at the time of this study, and all submitted to the same regular hemodialysis program 3 times a week.

The patients were examined twice (each time before hemodialysis), before and after 3 days of treatment with Aldactazine®, the combination diuretic (spironolactone [25 mg] and altizide [15 mg]) given orally as 1 tablet per day.

The examinations included (1) monitoring of all hemodynamic parameters: measurement of the right atrial, pulmonary arterial and capillary wedge pressures (RAP, PAP, PCWP, respectively) by a Swan-Ganz catheter;

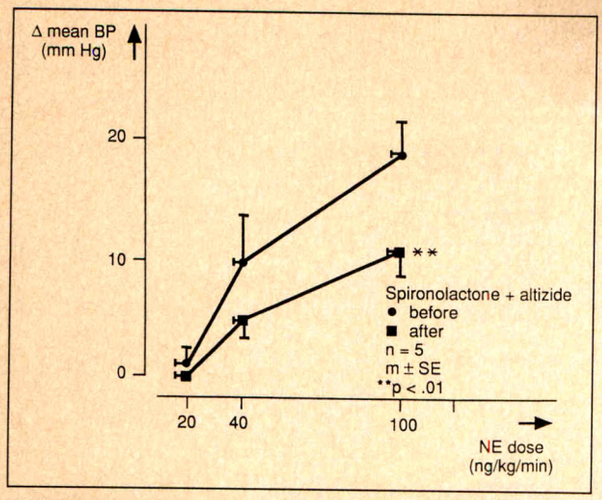


FIGURE 1. Dose-response relation between infused norepinephrine (NE) and changes in mean blood pressure (BP) before and after a short-term course of diuretics (3 days, spironolactone + altizide) in patients undergoing chronic dialysis. M ± SE = mean ± standard error of the mean.

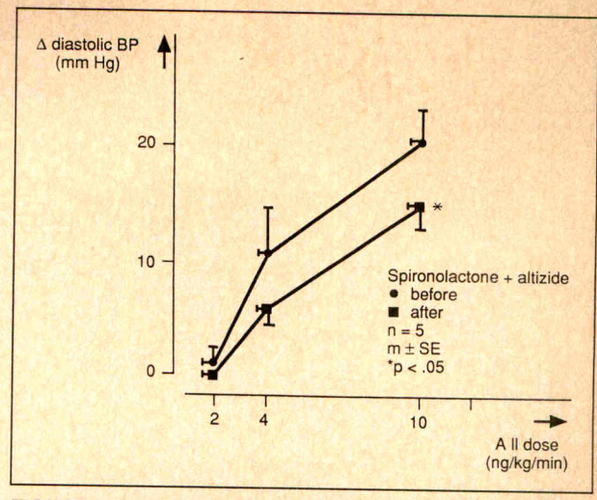


FIGURE 2. Dose-response relation between infused angiotensin II (AII) and changes in diastolic blood pressure (BP) before and after a short-term course of diuretics (3 days, spironolactone + altizide) in patients undergoing chronic dialysis. M ± SE = mean ± standard error of the mean.

measurement of the cardiac index (thermodilution, in triplicate), of the arterial pressure by cuff manometer, and of the heart rate; calculation of the systemic vascular resistances and of stroke index[7] (the catheter was indwelled 30 minutes before the measurements were taken); (2) study of the cardiovascular reactivity to infusion of incremental doses of NE (20, 40 and 100 ng/kg/min) and to infusion of incremental doses of AII (2, 4 and 10 ng/kg/min), performed according to our standard and procedure described elsewhere.[8] In addition to the changes in the arterial pressure induced by the infusion at the increasing stepwise doses of NE and AII, we recorded the variations of RAP and PCWP to analyze simultaneously the responsiveness of the venous capacitance and pulmonary vascular system;* and (3) the determination of serum chemistry parameters (creatinine, sodium, potassium, calcium, bicarbonate, chloride) and of the plasma levels of NE, renin activity and AII.[8]

Statistical analysis included paired and unpaired (2-tailed) Student *t* test, regression analysis and analysis of variance. The results are expressed as mean ± standard deviation or ± standard error of the mean. Because natural logarithmic transformation rather than absolute values followed Gaussian distribution for statistical analysis, we used the natural logarithmic transformation of NE and AII levels and dose of infused NE or AII.

TABLE I Effects of a Short-Term Course of Diuretics (3 Days, Spironolactone + Altizide) on Cardiovascular Reactivity to Infused NE and AII in Patients Undergoing Chronic Dialysis

	Spironolactone + Altizide (mean ± SD)	
	Before	After
No. of pts.	5	5
Norepinephrine Infusion		
Preinfusion plasma NE (ng/dl)	45.2 ± 17.1	43.1 ± 15.3
Pressor dose (ng/kg/min)	213 ± 58	428 ± 67†
Threshold dose (ng/kg/min)	22.4 ± 4.6	28.3 ± 3.1*
Slope of the curve	20.8 ± 4.1	16.1 ± 2.7*
Angiotensin II Infusion		
Preinfusion PRA (ng/ml/hour)	6.3 ± 1.8	6.1 ± 2.3
Preinfusion plasma AII (ng/dl)	22.6 ± 11	24.3 ± 7.1
Pressor dose (ng/kg/min)	22.4 ± 3.6	59.1 ± 4.4*
Threshold dose (ng/kg/min)	2.1 ± 0.4	2.9 ± 0.7
Slope of the curve	21.1 ± 3.4	13.2 ± 3.1*

Student *t* test, * $p < 0.05$, † $p < 0.01$.
AII = angiotensin II; NE = norepinephrine; PRA = plasma renin activity; SD = standard deviation.

TABLE II Hemodynamic Parameters Before and After a Short-Term Course of Diuretics (3 Days, Spironolactone + Altizide) in Patients Undergoing Chronic Dialysis

	Spironolactone + Altizide (mean ± SD)	
	Before	After
No. of pts.	5	5
Body weight (kg)	68.1 ± 9	68.5 ± 12
BP (mm Hg)		
systolic	166 ± 13	161 ± 10
diastolic	97 ± 7	90 ± 7*
Heart rate (beats/min)	72 ± 4	78 ± 4
RAP (mm Hg)	5 ± 2	4 ± 2*
PAP (mm Hg)	24 ± 3	22 ± 5
PCWP (mm Hg)	14 ± 4	13 ± 6*
Cardiac index (liters/min/m^2)	3.82 ± 0.63	3.73 ± 0.47
SVR (dynes s cm^{-5})	1,388 ± 217	1,317 ± 194

* Student *t* test, $p < 0.05$.
BP = blood pressure; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; SD = standard deviation; SVR = systemic vascular resistance.

*Low-pressure system.

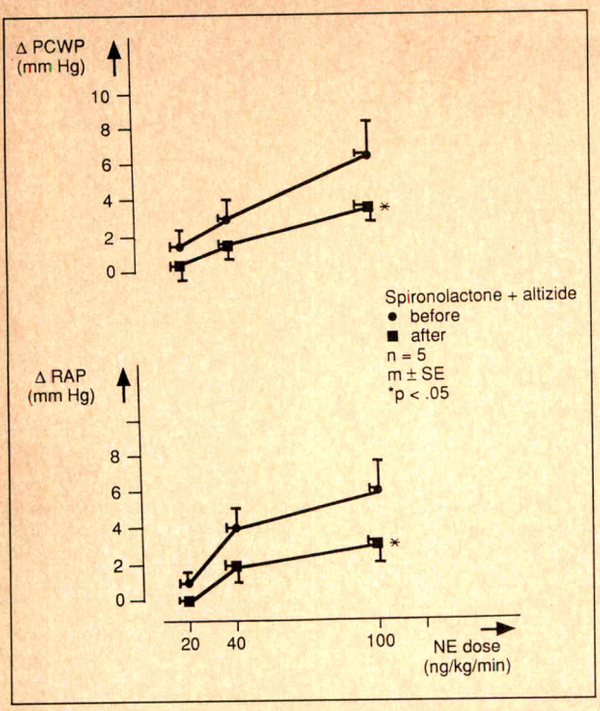


FIGURE 3. Dose-response relation between infused norepinephrine (NE) and changes in mean right atrial pressure (RAP) and mean pulmonary capillary wedge pressure (PCWP) before and after a short-term course of diuretics (3 days, spironolactone + altizide) in patients undergoing chronic dialysis. M ± SE = mean ± standard error of the mean.

RESULTS

Figures 1 and 2 show vascular reactivity to NE and AII. There was a marked dose-response relation between the vasopressor agents and mean (NE) or diastolic (AII) arterial BP. Short-term treatment with the diuretic combination significantly decreased reactivity of the high-pressure system* to the NE and AII infusions, as evidenced by the decrease in the slope of the curves (Table I). Compared with baseline, the diuretic combination moderated the increase in mean (NE) or diastolic (AII) BP induced by NE or AII. The pressor doses of NE and AII, which are also parameters of vascular reactivity, were significantly increased after diuretic treatment (+101% for NE, $p < 0.01$; +163% for AII, $p < 0.05$). Heart rate decreased in response to the NE-induced increase in mean BP; after treatment with the combination diuretic, heart rate decrease induced by the increase in mean BP after NE infusion, was less marked (−7 ±3 beats/min baseline vs −11 ±3 beats/min after treatment, $p < 0.05$).

Short-term treatment with Aldactazine in patients undergoing chronic hemodialysis modifies the hemodynamic parameters only slightly.

The arterial pressure decreases after treatment with Aldactazine; however, the decrease reaches statistical significance only for the diastolic arterial pressure (−7%, $p < 0.05$, Table II). The mean arterial pressure decreased by 7%. All the pressures of the low-pressure system, RAP, PAP and PWP, tended to decrease after Aldactazine without reaching statistical significance. The cardiac index decreased only slightly, despite the decrease of the stroke index, by an increase in heart rate, suggesting compensation by the baroreflex arc.

The decrease in arterial pressure is obtained by the decrease of the systemic vascular resistance and by the absence of a compensatory modification of the cardiac index.

Body weight is not significantly different between the treatment periods.

In response to NE infusion, RAP and PCWP increased along with arterial BP. After diuretic treatment, there was a significant decrease of the slope of the relation between RAP and PCWP and the infused NE and AII dose (Fig. 3).

Short-term treatment with spironolactone/altizide had no effect on preinfusion plasma levels of NE, AII, plasma renin activity, or on any clinical chemistry value (Table III).

TABLE III Effects of a Short-Term Course of Diuretics (3 Days, Spironolactone + Altizide) on Clinical Laboratory Values in Patients Undergoing Chronic Dialysis

	Spironolactone + Altizide (mean ± SD)	
	Before	After
No. of pts.	5	5
Plasma creatinine (mg/dl)	13.6 ± 1.7	13.5 ± 2.1
Sodium (mEq/liter)	137 ± 6	138 ± 4
Potassium (mEq/liter)	4.7 ± 0.3	4.9 ± 0.6
Chloride (mEq/liter)	103 ± 6	104 ± 5
Bicarbonate ion (mEq/liter)	19 ± 4	20 ± 3
Calcium (mg/liter)	93 ± 6	95 ± 5

SD = standard deviation.

DISCUSSION

This study was performed in patients undergoing chronic dialysis to demonstrate the specific vascular effects of 2 diuretics used in combination (spironolactone + altizide) and to avoid any possible effect of a negative sodium and water balance on the vascular system. We demonstrated the validity of this technique in a previous study of the nonrenal vascular effects of loop diuretics.[5]

Although the spironolactone dose was very low (25 mg), serum potassium was carefully monitored throughout the study and did not appreciably vary during the study (Table III).

Short-term treatment with this diuretic combination induced only slight changes in hemodynamic parameters. However, there was a significant decrease in diastolic BP, mainly due to a decrease in systemic vascular resistance that was not compensated for by the cardiac index. It can be assumed that the slight decrease in the cardiac index is a consequence of the reduced right atrial and pulmonary capillary pressures.

Cardiovascular response to infusion of NE and AII is an accurate measurement of the specific vascular effects of diuretics. The factors influencing cardiovascular reac-

*Arteriole-arterial system (resistance system).

tivity to these vasopressor agents are well known. These include changes both in water/electrolyte balance and in preinfusion plasma levels of these agents, and drugs. In this study, the preinfusion plasma levels of NE, renin activity and AII were all unchanged after diuretic treatment, compared with baseline. Body weight and plasma electrolytes were also virtually the same. Therefore, the changes in cardiovascular reactivity to NE and AII have to be a result of the specific effects of the diuretic combination on the cardiovascular system. The combination of spironolactone and altizide decreased vascular reactivity of both the low- and high-pressure system, which suggests that this diuretic combination, as has been found with loop diuretics, may increase venous and arterial compliance.[5,6]

In vitro studies in many different isolated tissues have shown that thiazide diuretics and spironolactone have specific vasorelaxant effects.[3–9] In vivo studies in humans have shown that the antihypertensive effect of spironolactone is largely associated with vasodilation.[6–10] These studies demonstrated that the vasodilator mechanism is a decreased responsiveness to exogenous stimuli, such as NE.[6–10] However, most of these investigations have explored only the reactivity vs the autonomic nervous system and not vs the renin-angiotensin system.

The mechanisms by which diuretics, including thiazides and spironolactone, affect the vascular reactivity of both the resistance and the capacitance vessels are still poorly understood. There is, however, some evidence that these agents, particularly spironolactone, may affect electrolyte transport (particularly sodium and calcium ions)[11] across vascular smooth muscle cell membranes. The possible role of prostaglandins has also been postulated.[12]

The results of our study suggest that the antihypertensive effect of spironolactone/altizide is mainly due to its direct action on resistance and capacitance vessels.

REFERENCES

1. National High Blood Pressure Education Program, National, Heart, Lung, and Blood Institute. The 1988 report of the National Committee on Detection, Evaluation and Treatment of high blood pressure. *Arch Intern Med 1988;148: 1023–1038.*

2. Freis ED. How diuretics lower blood pressure. *Am Heart J 1983;106:185–187.*

3. Materson BJ, Oster JR, Michaël VF, Bolton SM, Burton ZC, Stambaugh JE, Morledge J. Dose-response to chlorthalidone in patients with mild hypertension: efficacy of a lower dose. *Clin Pharmacol Ther 1978;24:192–198.*

4. Imbs JL, Schmidt M, Giesen-Crouze EM. Pharmacology of loop diuretics: state of the art. In: Grunfeld JP, Maxwell MH, Bach JF, Crosnier J, Funck-Brentano JL, eds. Advances in Nephrology. *Chicago: Year Book Medical, 1987;16:137–168.*

5. Jahn HA, Schohn DC. Cardiovascular effects of loop diuretics. In: Puschett JB, Greenberg A, eds. Diuretics II, Chemistry, Pharmacology and Clinical Applications. *NY: Elsevier Science, 1987;325–331.*

6. Clement DL. Effect of spironolactone on systemic blood pressure, limb blood flow and response to sympathetic stimulation in hypertensive patients. *Eur J Clin Pharmacol 1982;21:263–267.*

7. Schohn DC, Schmidt RL, Jahn HA. Malignant hypertension in end-stage renal failure: hemodynamic and hormonal status. Contr. to Nephrol. *Basel: Karger, 1985;49:185–192.*

8. Schohn DC, Weidmann P, Jahn HA, Beretta-Piccoli C. Norepinephrine-related mechanism in hypertension accompanying renal failure. *Kidney Int 1985;28:814–822.*

9. Weber MA, Purdy RE, Drayer JIM. Interactions of mineralocorticoids and pressor agents in vascular smooth muscle. *Hypertension, 1983;7:41–46.*

10. Mendlowitz M, Naftchni NE, Gitlow SE, Wolff RL. The effects of spironolactone on digital vascular reactivity in essential hypertension. *Am Heart J 1968;76:795–798.*

11. Hendry MB, Ellory JC. Molecular sites for diuretic action. *Trends Pharmacol Sci 1988;9:416–421.*

12. Johnston GD, Hiatt WR, Nies AS, Payne SA, Murphy RC, Gerber JG. Factors modifying the early non diuretic vascular effects of furosemide in man: the possible role of renal prostaglandins. *Circ Res 1983;53:630–635.*

Editorial Overview: European Experience with Spironolactone and Thiazide Diuretic as Antihypertensive Therapy

David P. Lauler, MD

For many years it has been appreciated that combination therapy with spironolactone and a diuretic offers additive benefits in the treatment of patients with edema disorders or in patients with hypertension. Spironolactone exerts its unique and competitive antagonism of aldosterone at receptor sites in the distal tubule, causing a mild natriuresis while conserving potassium and magnesium. Thiazide-type diuretics act at a different site in the distal tubule—a cortical diluting segment—and thereby potentiate the natriuretic action of spironolactone.

When used as a combination product, spironolactone generally minimizes the potassium and magnesium loss often seen with the use of thiazide diuretics as monotherapy in the treatment of patients with hypertension. Because fixed combinations of hypertensive products have not met with favor in this country, recommendations are usually made that such fixed combinations not be used for initial antihypertensive therapy; rather, the general advice is to titrate the individual components and switch to the appropriate combination dose after titration of the individual components.

In practice, this generally complicates the practice habits of the prescribing physician and also requires patients to take additional doses of medications during the titration phase, thus increasing the possibility of noncompliance by the patients.

Our European colleagues, particularly in France and Belgium, widely prescribe the combination product (Aldactazine®) of spironolactone and a thiazide diuretic (Altazide). This series of short clinical reports documents their favorable experience using such a fixed-dose combination as antihypertensive therapy. Dueymes reports on an open, randomized, multicenter trial involving 946 patients treated with 1 or 2 tablets daily of the combination product containing spironolactone, 25 mg, and altizide, 15 mg. At the end of the 90-day follow-up period, 80% of the hypertensive patients were successfully controlled with a minimum of major adverse reactions. These findings are further extended by the observations of Sternon, who reports on an ambulatory, multicenter study involving 780 patients placed into 2 study groups. The first group received spironolactone and altizide, 2 tablets daily, while the second group received the same combination spironolactone agent plus an additional antihypertensive agent (β blocker, alphamethyldopa or clonidine). Blood pressure reduction reached favorable levels in the first group (treated with the aldactone and altizide combination). More normal levels were reached in the second group, with the addition of the other antihypertensive agents, especially clonidine.

The nephrologists from Hôpital Necker in Paris, led by Grünfeld, discussed the fixed-dose combination form of spironolactone and altizide used as an antihypertensive agent compared with the antihypertensive action of the converting-enzyme inhibitor enalapril, in a randomized, double-blind, parallel-group study of 186 patients with moderate essential hypertension. These clinical investigators noted that both agents had comparable efficacy regarding blood pressure–reducing properties; they also noted that the converting enzyme inhibitor seemed to have more favorable antihypertensive action in patients younger than age 50 years, whereas spironolactone/altizide exhibited a greater benefit in patients older than 50.

Poncelet et al reported on a multicenter study of 53 patients, using ambulatory blood pressure–monitoring techniques comparing the antihypertensive action of spironolactone/altizide when used alone vs the addition of either enalapril or the β blocker acebutolol for patients requiring additional therapy. They reported that blood pressure was normalized in 23 of the 53 patients treated with spironolactone/altizide by the end of 4 weeks and was not in the remaining patients. The addition of either enalapril or acebutolol was equally effective in decreasing blood pressure. These investigators recommended that if a converting enzyme inhibitor is given to patients receiving the spironolactone/altizide combination product, a low dose such as 5 mg of enalapril should be chosen to prevent unwanted hypotensive reactions.

The final report by Henry et al is a comparative study of spironolactone (75 mg/day) vs a preparation of sustained-release nifedipine (40 mg twice daily). The antihypertensive response was comparable in both the spironolactone and calcium channel blocker groups. In patients not responding, therapy was switched to the alternate medications so that those who were receiving spironolactone then received concomitant nifedipine therapy; patients in whom nifedipine therapy was begun received

From Yale University School of Medicine, New Haven, Connecticut.
Address for reprints: David P. Lauler, MD, Lawrence and Memorial Hospital, Montauk Avenue, New London, Connecticut 06320.

concomitant spironolactone therapy. After 45 days, it was noted that 63% of the patients receiving combination therapy achieved normal blood pressure. Adverse effects were higher in the group receiving nifedipine therapy.

This collection of different antihypertensive trials involving spironolactone, or spironolactone in combination with altizide, expands our knowledge of the usefulness of these products as antihypertensive agents and provides direction for the judicious concomitant use of other mainline antihypertensive agents. The vascular activity of spironolactone also provides future direction for studies on vascular and ventricular remodeling, a suggestion enhanced by the recent information of spironolactone's inhibition of certain calcium channels.

Clinical Update: Spironolactone and Altizide as Monotherapy in Systemic Hypertension

Jean-Marc Dueymes, MD

A large-scale, open, nonrandomized, multicenter, 90-day study of the safety and efficacy of a thiazide diuretic and aldosterone antagonist combination (Aldactazine®, 25 mg spironolactone and 15 mg altizide, 1/day) as monotherapy was performed in 946 patients with mild to moderate hypertension (diastolic blood pressure [BP] between 90 and 120 mm Hg). Adverse effects were assessed, and body weight, heart rate, serum potassium, creatinine and uric acid measurements were monitored. On day 45 of the study, BP was normalized (diastolic BP ≤90 mm Hg) in 72% of the patients. The dose was increased to 2 tablets per day in the patients whose BP did not reach normal levels. By the end of the study, BP was controlled in 83% of the patients. No significant changes were noted in body weight, heart rate or laboratory values; however, treatment had to be discontinued in 6 patients because of hypokalemia (n = 4) or elevated serum creatinine levels (n = 2). Serum uric acid levels were increased in 5.5% of patients. The rate of adverse effects, as reported by the patients, was low (5%). Thus, this study demonstrates that diuretics, especially the combination of a thiazide diuretic and aldosterone antagonist, remain a safe, effective and economical therapy for patients with mild to moderate hypertension.

Am J Cardiol 1990;65:20K–23K)

From Service de Néphrologie et d'Hémodialyse, University of Toulouse, Toulouse, France.

Address for reprints: Jean-Marc Dueymes, MD, Centre d'Hémodialyse Pasteur, 17 rue A. Kervern, 29200 Brest, France.

The number of antihypertensive drugs is growing steadily. Recently, the therapeutic trend has been toward increased specificity (e.g., angiotensin-converting enzyme inhibitors, calcium antagonists); however, patients with hypertension often need long-term pharmacologic therapy, which mandates a drug that produces minimal side effects, does not interfere with a patient's quality of life, and is of moderate cost. Diuretics meet these criteria. This may explain why, after more than 30 years of use, they remain an integral part of the antihypertensive therapeutic regimen.[1] But even though diuretics have been proven to be well tolerated by many patients,[1,2] some, especially the thiazides, can cause various metabolic complications, such as hypokalemia and hypomagnesemia, which may lead to cardiac arrhythmias.[3,4] On the other hand, it is well known that a thiazide diuretic used in combination with an aldosterone antagonist will effectively reduce patients' blood pressure (BP).

Spironolactone, a direct aldosterone antagonist, helps counteract the thiazide-induced activation of the renin-angiotensin-aldosterone system and prevents subsequent potassium loss in the urine[5] without any adverse effect on serum lipids.[5] There is also evidence that spironolactone, in combination with a thiazide diuretic, can reverse diuretic-related hypokalemia.[6] A large-scale study of a thiazide-spironolactone combination (Aldactazine®) was performed to (1) confirm that the combination drug would effectively control BP in most hypertensive patients, and (2) assess the tolerability and safety of different doses of the combination.

METHODS

An open, nonrandomized, multicenter (150 participating physicians), 3-month study of 946 patients with mild to moderate hypertension (diastolic BP between 90 and 120 mm Hg) was performed. The study's progress was continuously monitored in real time by a computer linkup (Minitel).

Criteria: The study comprised men and women, aged 18 to 75 years, with untreated or treated mild to moderate hypertension (supine diastolic BP between 90 and 120 mm Hg, systolic BP ≥160 mm Hg). The exclusion criteria were pregnant or nursing women, need for concomitant antihypertensive therapy, renal failure (creatinine level >15 mg/liter), hepatic dysfunction, serum potassium >5.5 mEq/liter, hypersensitivity to thiazides or spironolactone, orthostatic hypotension (systolic BP decrease >40 mm Hg on standing, and concomitant treatment with calcium antagonists or β blockers.

Study schedule: The study was performed from May 1984 to May 1985. The patients were seen 3 times: at the

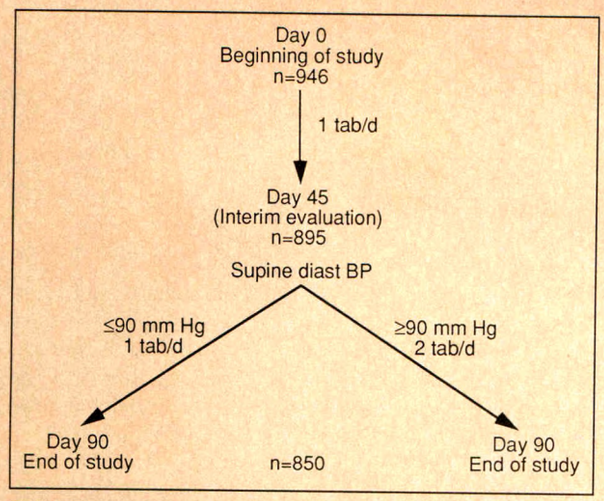


FIGURE 1. Study design. d = day; diast = diastolic; tab = tablet.

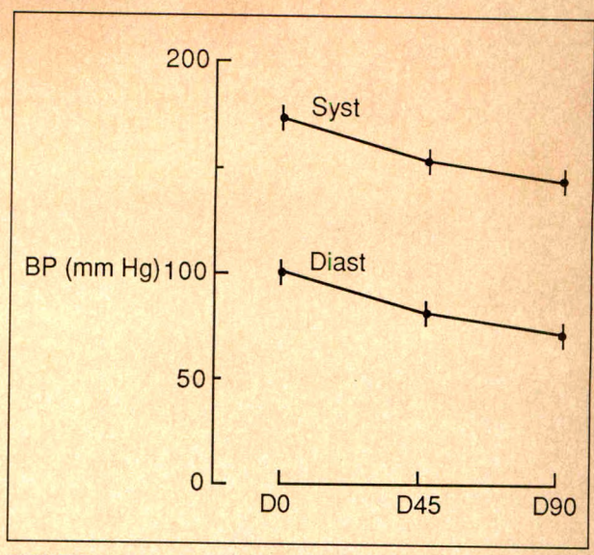


FIGURE 2. Effect of monotherapy with Aldactazine on blood pressure in 946 patients. BP = blood pressure; D = study day; Diast = diastolic; Syst = systolic.

beginning of the study (day 0, 946 patients), at day 45 (895 patients) and at day 90 (850 patients). At these visits, BP (systolic and diastolic, supine and standing), body weight and heart rate were recorded, as were serum potassium, creatinine and uric acid levels; complaints of adverse effects were noted (Fig. 1, Table I).

Dosage: The dosage was 1 tablet of Aldactazine (25 mg spironolactone, 15 mg altizide) per day, taken orally. At day 45 the dosage was increased to 2 tablets per day for those patients whose BP had not reached normal levels (supine diastolic BP >90 mm Hg [Fig. 1]).

Patient population: Initially, 1,012 case reports (562 women, 450 men) were studied. The patients ranged in age from 20 to 84 years (mean 61 ± 11, women 62 ± 11, men 60 ± 11). Mean body weight was 71 ± 13 kg (women 67 ± 13, men 76 ± 12).

Sixty-one percent of the patients had concomitant disease (cardiovascular, 12.5%; rheumatoid, 10.3%; endocrine, 5.9%). A family history of hypertension was noted in 42.6% of the patients, and 45.4% were currently being treated or had been treated with an antihypertensive drug. Hypertension had been present for less than 1 year in 283 patients (28%) and more than 3 years in 438 patients (43.3%).

RESULTS

Population: Of the 1,012 patients, 66 were dismissed from the evaluation because they did not meet protocol criteria (age, BP, or laboratory values outside the study ranges). Thus, 946 case reports were used for the evaluation of safety and efficacy. Some patients were not present for the day 45 and day 90 visits. These patients were included in the evaluation, but were considered therapeutic failures, as were 6 patients who discontinued treatment after day 45 because of elevated creatinine levels (n = 2) or hypokalemia (n = 4). Consequently there were 946 patients on day 0, 895 on day 45, and 850 on day 90 (Fig. 1).

Blood pressure: At day 0, mean systolic (supine) and diastolic BP was 177 ± 13 and 101 ± 8 mm Hg, respectively. Mean values for serum potassium, creatinine and uric acid were 4.3 ± 0.4 mEq/liter, 10.5 ± 2 mg/liter, and 57 ± 14 mg/liter, respectively (Fig. 2, Table I).

On day 45, BP was normalized (diastolic BP ≤90 mm Hg) in 680 of the patients (72%). Dosage had to be increased to 2 tablets per day in 210 patients (22%). Of these 210 patients, 199 returned for the day 90 visit, and BP had normalized in 152 (diastolic BP ≤90 mm Hg). By the end of the 90-day study, BP had normalized in 83% of the patients (786 of 946).

Body weight and heart rate: There were no significant changes in body weight and heart rate between day 0 and day 45, day 45 and day 90, and day 0 and day 90 (Table I).

Laboratory values: Overall, no significant changes were observed in serum potassium (mean 4.28 ± 0.42 mEq/liter, day 0, vs 4.28 ± 0.38 mEq/liter, day 90), creatinine (mean 10.47 ± 2.09 mg/liter, day 0, vs 10.59 ± 2 mg/liter, day 90), or uric acid levels (mean 56.67 ± 13.94 mg/liter, day 0, vs 57.33 ± 13.1 mg/liter, day 90). However, treatment was discontinued in 4 patients on

TABLE I Change in Blood Pressure, Heart Rate, Body Weight and Laboratory Values from Baseline (Day 0) to End of the Study

	Day 0	Day 45	Day 90
Syst BP (supine, mm Hg)	177 ± 13	157 ± 14	151 ± 13
Diast BP (supine, mm Hg)	101 ± 8	89 ± 9	84 ± 7
Syst BP (standing, mm Hg)	175 ± 14	155 ± 15	150 ± 13
Diast BP (standing, mm Hg)	101 ± 9	88 ± 9	84 ± 7
Heart rate (supine, beats/min)	77 ± 10	76 ± 8	75 ± 8
Body weight (kg)	71 ± 13	70 ± 13	70 ± 13
Serum creatinine (mg/liter)	10.5 ± 2	10.5 ± 2	10.6 ± 2
Serum uric acid (mg/liter)	57 ± 14	57 ± 13	57 ± 13
Serum potassium (mEq/liter)	4.3 ± 0.4	4.3 ± 0.4	4.3 ± 0.4
No. of pts	946	895	850

BP = blood pressure; Diast = diastolic; Syst = systolic.

TABLE II Subgroup Analysis

	No. of Pts.	Day 90 Diast BP <90 mm Hg
Previous antihypertensive treatment	336/375	89.6%
No previous antihypertensive treatment	399/424	94.1%

BP = blood pressure; Diast = diastolic.

TABLE III Side Effect Profile (n = 912)

No adverse effects	865 (95%)
Fatigue	11 (1.2%)
Gastrointestinal disturbances	10 (1.1%)
Orthostatic hypotension	4 (0.44%)
Gynecomastia	2 (0.22%)

n = number of case reports.

day 45 because of hypokalemia (3.0, 3.2, 3.3 and 3.4 mEq/liter, respectively), and 5 patients were hypokalemic on day 90 (3.2, 3.3, 3.4 and 3.4 mEq/liter, respectively). On day 0, serum creatinine levels were >15 mg/liter in 9 patients. However, no significant change in renal function was noted in these patients when they were seen again on days 45 and 90. But increased serum creatinine levels were detected in 4 patients with normal renal function (16, 19, 19 and 16 mg/liter) on day 45, and in 2 on day 90 (16 and 20 mg/liter). Two of the 4 patients with elevated creatinine on day 45 withdrew from the study, and creatinine levels were normal in the other 2. Uric acid levels were increased in 5.5% of the patients (Table I).

SUBGROUP ANALYSIS

The results were also analyzed after dividing the patients into different subgroups according to drug dosage, age, or previous antihypertensive treatment. After excluding patients who did not meet all protocol criteria, or for whom some data were missing, 799 case reports were evaluated.

Dosage: In the patients who continued to take 1 tablet per day (group A) (25 mg spironolactone, 15 mg altizide) for the duration of the study, mean supine diastolic BP decreased from 99 ± 8 to 83 ± 6 mm Hg between day 0 and day 90. On average, systolic BP decreased from 174 ± 13 to 148 ± 11 mm Hg.

In those patients whose diastolic BP had not normalized (diastolic BP >90 mm Hg) on day 45 and who were given the 2-tablets-per-day regimen (group B), mean diastolic BP decreased from 105 ± 8 to 89 ± 9 mm Hg, between day 0 and day 90, and average systolic BP decreased from 181 ± 15 to 157 ± 15 mm Hg (Table II).

This breakdown provides no dose-effect information because the 2 groups are not comparable. BP values in the group B patients were already higher on day 0 (e.g., diastolic BP was 105 ± 8 vs 99 ± 8 mm Hg). Also, 56.9% of the patients in group B had been previously treated for hypertension vs 43.9% of the patients in group A. No significant differences, however, were noted in the laboratory values between the 2 groups.

Age and no previous antihypertensive treatment: Of 799 patients, 375 (46.9%) had been previously treated for hypertension. Among these 375, diastolic BP was under control (≤90 mm Hg) on day 90 in 336 or 89.6% (Table II). The dosage was increased to 2 tablets per day in 85 of the 375 patients (22.6%).

Among these 375 patients, 63 were younger than age 55 years. On day 90, diastolic BP was still >90 mm Hg in 8 of the 63 younger patients (5 of these 8 patients had been on the 2-tablets-per-day regimen). Among the older patients (over 55 years), BP had not normalized on day 90 in 31 cases despite increased dosage in 22 of the 31.

Age and previous antihypertensive treatment: Of the 799 patients, 424 (53%) had not been previously treated for hypertension. Among these, BP was controlled (diastolic BP ≤90 mm Hg) on day 90 in 399 or 94.1% (Table II). The dosage was increased to 2 tablets per day in 63 of the 424 patients on day 45 (14.9%).

In this subgroup, 151 patients (36.5%) were younger than age 55 years, and diastolic BP was >90 mm Hg in 12 of them on day 90 despite the dose increase in 11 of the 12. The other 273 patients (64.4%) of this subgroup were older than 55. By the end of the study, BP was still >90 mm Hg on day 90 in 13 patients despite the higher dose in 7 of the 13.

Adverse effects: Complaints of adverse effects were recorded for 912 patients; however, the drug was well tolerated by 865 (95%). The adverse effects reported by the remaining 47 patients (5.1%) were minor, including fatigue (n = 11), gastrointestinal disturbances (n = 10), orthostatic hypotension (n = 4) and gynecomastia (2 cases) (Table III).

DISCUSSION

The purpose of this study was to evaluate the safety and efficacy of Aldactazine as monotherapy in a large (over 1,000 patients) and heterogeneous population of hypertensive patients. For this reason the selected investigators were family practitioners who entered their own ambulatory hypertensive patients.

Interpretation of the study results, however, should include accounting for the limitations and constraints imposed by the protocol. This was an open, nonrandomized study with flexible inclusion criteria and study conditions. Because of this flexibility, compliance with study protocol was excellent, and a large number of case reports could be evaluated (946). On average, the patients were relatively old (49.8% over age 60 vs 27.2% under age 55), of normal weight (76.4 kg for the men), and had had hypertension for more than 3 years (43.3% of the cases). This was not a randomly selected hypertensive population, but one selected according to the investigators' particular clinical experience.

Results confirm that monotherapy with Aldactazine is effective; by the end of the study, BP was controlled in over 80% of the patients (mean supine systolic and diastolic BP 151 and 85 mm Hg, respectively).

A biased interpretation of the study results is possible, since the age distribution was nonhomogeneous. The ef-

fectiveness criterion was based on supine diastolic pressure. On day 90, 27.3% of the patients had a diastolic BP of 90 mm Hg, and 65.2% had a diastolic BP <90 mm Hg. Between day 0 and day 90, BP decreased from 173/100 to 143/83 mm Hg in patients younger than age 55 years and from 177/99 to 151/83 mm Hg in those older than 55; therefore, age should be taken into account with these figures. A diastolic BP of 90 mm Hg, although fully satisfactory in a 65-year-old patient, may not be satisfactory in a 40-year-old patient.

Because of methodologic constraints (no randomization on day 45) and because the 2 groups on the 1- or 2-tablets-per-day regimen are not comparable in terms of the severity of hypertension, we were unable to assess a dose-effect relation. By day 90, BP had normalized in 35.2% of the 199 patients whose dose was increased to 2 tablets per day. This could be due to the increase in dose or could have occurred with the initial dosage.

Laboratory values remained essentially unaffected; however, because of the potential risk of elevated serum creatinine (5 cases) and hypokalemia, laboratory values should be monitored during the first few weeks of treatment with this drug.

CONCLUSIONS

This study demonstrates that diuretics, and particularly the combination of a thiazide diuretic and an aldosterone antagonist, continue to be effective therapy in moderate essential hypertension. For most patients, this therapy will be sufficient and has the advantage of a low rate of adverse reactions and low cost.

The goal of antihypertensive therapy is not limited to reducing BP, but also includes reducing the associated morbidity and mortality. Long-term epidemiologic studies have shown that both diuretics and β blockers are effective in this respect.[6,7,8] Because no comparable data currently exist on the long-term efficacy of the newer antihypertensive methods, diuretics and β blockers should remain as first-line therapy for the treatment of hypertension.[6,9]

REFERENCES

1. 1988 Joint National Committee. The 1988 Report of the Joint National Committee on detection, evaluation, and treatment of high blood pressure. *Arch Intern Med 1988;148:1023–1038.*

2. Cannon PJ. Diuretics: Their mechanism of action and use in hypertension. *Cardiovascular Reviews and Reports 1983;4:649–664.*

3. Wester PO, Dyckner T. Magnesium in cardiac failure and diuretic treatment. *Magnesium Bulletin 1986;8:204–209.*

4. Field MJ, Lawrence JR. Complications of thiazide diuretic therapy: An update. *Med J Aust 1986;144:641–644.*

5. Laragh JH. Modification of stepped care approach to antihypertensive therapy. *Am J Med 1984;77:78–86.*

6. Muller J. Spironolactone in the management of congestive heart failure: A review. *Clin Ther 1986;9:63–76.*

7. Multiple Risk Factor Intervention Trial Record Group. Multiple Risk Factor Intervention Trial: risk factor changes and mortality results. *JAMA 1982; 248:1465–1477.*

8. Shea S, Cook EF, Kannel WB, Goldman L. Treatment of hypertension and its effect on cardiovascular risk factor: Data from the Framingham Study. *Circulation 1985;71:22–30.*

9. Breckenridge A. Treating mild hypertension. *Br Med J 1985;291:89–90.*

Spironolactone and Altizide in Systemic Hypertension: Ambulatory Multicenter Study

Jacques Sternon, MD

A multicenter study was performed in 919 hypertensive patients, 780 of whom could be evaluated. Patients in group I (n = 482) were treated with Aldactazine® alone (altizide + spironolactone, 2 tablets per day). The other 298 patients (group II) were treated with 1 or 2 tablets per day of Aldactazine plus a conventional antihypertensive agent, e.g., a β blocker, α-methyldopa or clonidine. After 45 days of treatment with Aldactazine alone, mean systolic and diastolic blood pressure (BP) decreased by 15 and 14%, respectively, vs baseline values. The addition of the other antihypertensive agent decreased BP further; however, the best results were obtained with the combination of Aldactazine and clonidine. With this combination, systolic and diastolic BP decreased by 16.6 and 18%, respectively, vs baseline. In terms of adverse effects, a few cases of gastrointestinal disturbances and orthostatic hypotension were reported.

(Am J Cardiol 1990;65:24K–27K)

Thiazide diuretics have long been used as first-line pharmacologic therapy of essential hypertension.[1] However, they have been associated with a number of metabolic adverse effects such as hyperglycemia, hyperuricemia, hypertriglyceridemia, decreased high-density lipoprotein cholesterol, hypokalemia and hypomagnesemia.[2–4]

This has resulted in increased interest in potassium-sparing diuretics, particularly when combined with a thiazide diuretic, because this type of combination appears to be more devoid of metabolic consequences than the thiazides alone.[5,6]

This study was conducted to assess the efficacy of an aldosterone antagonist-altizide combination (Aldactazine®) and to compare its sole use vs its use with other antihypertensive agents in patients with essential hypertension.

METHODS

Patients: Patients considered for the study were male and female ambulatory patients, 20 to 85 years old, with essential hypertension (systolic and diastolic blood pres-

TABLE I Therapeutic Regimens

Add-On Antihypertensive	Aldactazine (1 tab/day)	Aldactazine (2 tab/day)	Total No. of Pts.
β blocker	42	83	125
α-Methyldopa	11	42	53
Clonidine	13	31	44
Other	21	55	76
Total	87	211	298

tab = tablet.

TABLE II Discontinuations, Protocol Violations, Adverse Effects*

Adverse Effects (n = 31)	Group I (n = 16)	Group II (n = 15)
GI disturbances	4	6
Syncope	4	3
Pollakiuria	3	—
Headaches	3	1
Muscle cramps	1	1
Pruritus	1	1
Lumbar pain	1	2
Constipation	1	—
Diarrhea	—	—
Dry mouth	—	1

* Protocol violations/dropouts (n = 107)
GI = gastrointestinal

From the ULB, Brussels, Belgium.

Address for reprints: Jacques Sternon, MD, Hôpital Universitaire Erasme, Service de Médicine Interne, Route de Lennik, 808, 1070 Bruxelles, Belgium.

TABLE III Group I: Distribution of Systolic Blood Pressure Values

Syst BP (mm Hg)	No. of Pts.	%
155	49	10
160–183	276	57
184–211	127	26
212+	30	6
Total	482	100

BP = blood pressure; Syst = systolic.

TABLE IV Group I: Distribution of Diastolic Blood Pressure Values

Diast BP (mm Hg)	No. of Pts.	%
95–102	184	42
103–116	171	39
117+	83	19
Total	438	100

BP = blood pressure; Diast = diastolic.

TABLE V Group I: Improvement in Systolic Blood Pressure After Monotherapy with Aldactazine (Statistical Approximation)*

Day 0 Systolic BP (mm Hg)	Day 45 20–39 Years (2 tab/day)	40–59 Years (2 tab/day)	60–89 Years (2 tab/day)
150	138.7	140.5	142.2
160	142.8	144.7	146.4
170	146.7	148.6	150.4
180	150.5	152.5	154.3
190	154.2	156.2	158.1
200	157.7	159.8	161.7
210	161.2	163.3	165.3
220	164.6	166.7	168.8

* The statistical approximation is the statistical value estimated under the hypothesis of the statistical model, i.e., $\mu(BP_{d45}/BP_{d0}) = \mu \log (BP_{d0}) + B +$ error. We selected this analysis of covariance because it seemed adequate for the variable to be predicted, given the fact that BP_{d45} was not integrable to a contingent variable. The effect of these parameters was determined, but not taken into consideration for group II, because of the large number of parameters and the small population.
BP = blood pressure; tab = tablet.

TABLE VI Group I: Improvement in Diastolic Blood Pressure

Day 0 (mm Hg)	Day 45 (mm Hg)
80	78.8
90	83.8
100	88.2
110	92.5
120	96.6
130	100.6
140	104.4
150	108.0

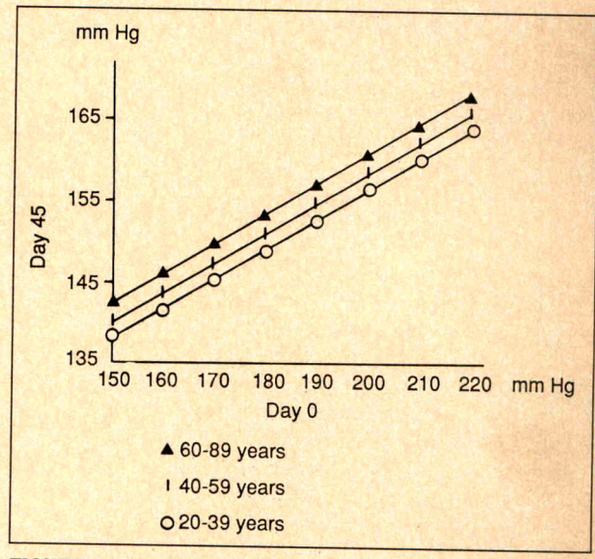


FIGURE 1. Systolic blood pressure.

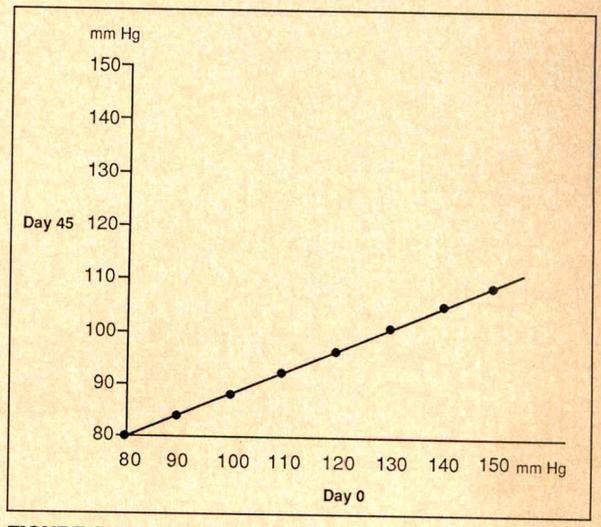


FIGURE 2. Diastolic blood pressure.

sure [BP] ≥150 and ≥95 mm Hg, respectively). All patients gave informed consent.

Criteria: Patients with kidney failure, anuria, hyperkalemia, hypersensitivity to thiazide diuretics, and pregnant or nursing women were excluded from the study.

Dosage and monitoring: The study comprised 2 groups: group I (Aldactazine as monotherapy)—2 tablets of Aldactazine per day with breakfast. Group II (combination therapy)—1 or 2 tablets of Aldactazine per day plus either a β blocker, α-methyldopa, clonidine, or other antihypertensive agent that the patient may have been using. Serial BP (seated) measurements were obtained by the same investigator after 15 and 45 days of treatment (control visits). Heart rate and adverse effects were similarly recorded.

Patient distribution: Initially, 919 patients were enrolled in the study. They were divided into 2 groups: (1) Group I was a monotherapy group consisting of 590 patients treated with 2 tablets of Aldactazine per day; of these, 482 came back for the 2 follow-up visits (Table I). (2) Group II was a combination therapy group consisting of 329 patients who received Aldactazine (1 or 2 tablets per day) plus either a β blocker, α-methyldopa, clonidine or another antihypertensive. Within group II, 298 patients came to the 2 follow-up visits (Table I).

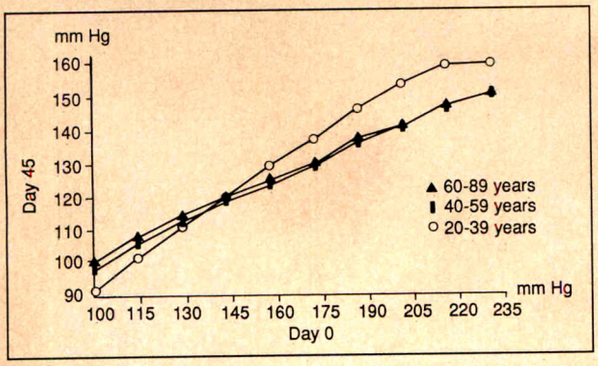


FIGURE 3. Double product.

TABLE VII Group II: Age-Related Distribution of Systolic Blood Pressure Values in Each Therapeutic Subgroup

Systolic BP (mm Hg)	20–39 Years	40–59 Years	60–89 Years	Total	%
Aldactazine + β Blocker					
≤159	4	3	1	8	6.4
160–184	7	36	19	62	49.60
185–214	3	25	17	45	36.00
≥215	1	4	5	10	8.00
Total	15	68	42	125	
%	12	54.40	33.60		100
Aldactazine + α-Methyldopa					
≤159	0	0	0	0	0
160–184	3	12	13	28	52.8
185–214	0	7	11	18	34.0
≥215	0	2	5	7	13.2
Total	3	21	29	53	
%	6	39.6	54.7		100
Aldactazine + Clonidine					
≤159	0	1	2	3	6.8
160–184	1	7	11	19	43.2
185–214	1	4	10	15	34.1
≥215	0	2	5	7	15.9
Total	2	14	28	44	
%	4.5	32	63.6		100

BP = blood pressure.

Of the initial 919 patients, 31 withdrew from the study because of adverse effects (16 from group I and 15 from group II). In addition, 107 patients were withdrawn from the study for protocol violations (Table II).

TABLE VIII Group II: Age-Related Distribution of Diastolic Blood Pressure Values in Each Therapeutic Subgroup

Diastolic BP (mm Hg)	20–39 Years	40–59 Years	60–89 Years	Total	%
Aldactazine + β Blocker, Middle-Sized Dose					
≤95	3	8	3	14	10.8
96–104	11	17	19	47	36.1
105–119	4	25	13	42	32.3
≥120	2	18	7	27	20.8
Total	20	68	42	130	
%	15.4	52.3	32.3		100
Aldactazine + α-Methyldopa (750 mg/day)					
≤95	0	1	8	9	17.0
96–104	2	7	7	16	30.2
105–119	1	9	7	17	32.1
≥120	0	4	7	11	20.8
Total	3	21	29	53	
%	5.7	39.6	54.7		100
Aldactazine + Clonidine (450 μg/day)					
≤95	0	2	3	5	11.4
96–104	0	0	6	6	13.6
105–119	1	7	12	20	45.4
≥120	1	5	7	13	29.5
Total	2	14	28	44	
%	4.5	31.8	63.6		100

BP = blood pressure.

Statistical evaluation: Statistical analysis was performed on the variations in systolic and diastolic BP values on day 0 and day 45 for 780 patients divided into 2 groups (monotherapy and add-on therapy).

RESULTS

Group I (monotherapy): Baseline systolic BP varied between 160 and 210 mm Hg in 83% of the cases (Table III). Baseline diastolic BP ranged between 95 and 116 mm Hg in 81% of the patients (Table IV). There was a marked reduction in systolic BP between day 0 and day 45. The variations in systolic BP between day 0 and day 45, broken down by age group, are listed in Table V. The systolic BP profiles between day 0 and day 45 were parallel for the various age groups, with the lower readings, as expected, in the younger age group (Fig. 1).

TABLE IX Percent Change in Blood Pressure at Day 45 vs Day 0

	Systolic BP			Diastolic BP		
	Mean (%)	Range* (%)	No. of Pts.	Mean (%)	Range* (%)	No. of Pts.
Group I Aldact alone	14.3	13.6–15.0	482	13.4	12.7–14.1	498
Group II						
β blocker	15.4	12.0–17.0	125	15.5	13.8–17.2	130
α-methyldopa	16.0	13.9–18.2	53	14.5	11.2–17.6	53
Clonidine	16.6	13.5–19.6	44	18	14.4–21.6	44
Other	12.9	11.0–14.7	75	14.8	12.7–16.8	76

* 95% confidence interval.
Aldact = Aldactazine; BP = blood pressure.

Diastolic pressure decreased greatly between day 0 and day 45 (Table VI). The statistical analysis of diastolic BP variations confirmed this decrease (Fig. 2). Diastolic BP values were not broken down into the different age groups.

Statistical analysis showed that age had an effect on double product (systolic BP × heart rate) as well (Fig. 3). The best results were obtained in hypertensive patients older than 60 years.

Group II (combination therapy): Tables VII and VIII show the distribution of BP values as a function of age in the 3 therapeutic subgroups (Aldactazine + β blocker, Aldactazine + α-methyldopa, and Aldactazine + clonidine).

Both systolic and diastolic BP decreased very markedly between day 0 and day 45. Statistical analysis shows the benefits of the combination of Aldactazine and the various antihypertensive agents (β blocker, methyldopa, or clonidine) vs monotherapy with Aldactazine alone (Table IX). Although significance could not be determined because of the lack of a suitable control group, the combination of Aldactazine and clonidine was especially effective, particularly since the patients in this subgroup were older and had relatively higher BP levels than those in the other subgroups (Table IX).

The statistical analysis of the double product showed that combination therapy, especially Aldactazine plus β blocker, was particularly effective, presumably because of the bradycardiac effect of the β blocker (Table X).

TABLE X Percent Change in Double Product Between Day 45 and Day 0

	Mean (%)	Range* (%)	No. of Pts.
Group I Aldact alone	17.2	16.1–18.3	488
Group II			
β blocker	24.1	21.3–26.8	114
α-methyldopa	21.0	17.9–23.9	45
Clonidine	20.0	15.1–24.6	36
Other	17.4	14.2–20.5	69

* 95% confidence interval.
Aldact = Aldactazine.

ADVERSE EFFECTS

A number of minor adverse effects were recorded in each group, consisting mostly of gastrointestinal disturbances and orthostatic hypotension (Table XI). One patient with gout in group I had an attack during the treatment period.

CONCLUSIONS

Although the absence of a control group precluded calculations of statistical significance, the results of this large multicenter study demonstrate that a combination product of aldosterone antagonist (spironolactone) is both safe and effective in the treatment of hypertension, whether used alone or when combined with other "add-on" antihypertensive agents (β blockers, methyldopa, clonidine).

REFERENCES

1. Joint National Committee. The 1988 report of the Joint National Committee on detection, evaluation, and treatment of high blood pressure. *Arch Intern Med 1988;148:1023–1038.*
2. Dreslinski GR, Frohlich ED, Messerli FH, Batson HM. Diuretics. *Practical Cardiology 1980;6:132–145.*
3. Hollifield JW. Thiazide treatment of hypertension: effects of thiazide diuretics on serum potassium, magnesium, and ventricular ectopy. *Am J Med 1986;80: suppl 4A:8–12.*
4. Whang R. Magnesium deficiency: pathogenesis, prevalence, and clinical implications. *Am J Med 1987;72:suppl 3A:24–29.*
5. Dyckner T, Wester PO. Potassium/magnesium depletion in patients with cardiovascular disease. *Am J Med 1987;82:suppl 3A:11–17.*
6. Muller J. Spironolactone in the management of congestive cardiac failure: a review. *Clin Ther 1986;9:63–76.*

TABLE XI Adverse Effects with Each Therapeutic Regimen

Adverse Effects	Group I Monotherapy (482 Patients): Aldactazine	Group II Combination Therapy Add-On (293 Patients)		
		β Blocker	α-Methyldopa	Clonidine
GI disturbances	18	6	2	3
Orthostatic hypotension	16	7	1	2
Weakness	8	1	—	1
Muscle cramps	4	3	1	1
Headache	3	3	—	—
Pollakiuria	2	—	—	—
Gynecomastia, mild	2	—	—	1
Thirst	1	—	—	—
$K^{+}\uparrow$	1	—	—	—
$K^{+}\downarrow$	1	—	—	—
Dry mouth	—	—	1	—
Diarrhea	1	—	—	—
Constipation	1	—	—	—
Sleep disturbances	1	—	—	—
Skin rash	—	—	1	—
Visual disturbances	—	1	—	—
Gout	1	—	—	—

GI = gastrointestinal; $K^{+}\uparrow\downarrow$ = potassium increased and decreased.

Spironolactone and Altizide Versus Converting Enzyme Inhibitor (Enalapril)

Jean-Pierre Grünfeld, MD, Marie Wehrlen, MD, Bruno Pelletier, MD, and Michel-Hubert Capron, MD

The safety and antihypertensive effectiveness of a fixed-dose combination form of spironolactone + altizide (S/A) were compared with those of enalapril, an angiotensin-converting enzyme inhibitor in a randomized, double-blind, parallel-group study of 186 patients with moderate essential hypertension. The 2 treatment groups were comparable in terms of age, gender, duration and severity of hypertension, diastolic blood pressure (BP), serum potassium and creatinine, and 24-hour urinary sodium excretion after a 4-week washout phase. After 8 weeks of treatment, both S/A and enalapril decreased BP significantly and to about the same extent. Enalapril, however, was more effective in decreasing supine diastolic BP in patients younger than age 50, whereas S/A yielded better results in those older than 50. Laboratory values were similar after both drugs were administered, and there were no clinically significant changes. The study demonstrated that S/A safely reduces elevated BP, particularly in older patients.

(Am J Cardiol 1990;65:28K–32K)

From the Department of Nephrology, Hôpital Necker, Paris, and the Laboratories Searle, Boulogne-Billancourt, France.

Address for reprints: Bruno Pelletier, MD, Cardiovascular Department, Laboratories Searle, 52 rue Marcel Dassault, 92514 Boulogne-Billancourt, France.

For the past 3 decades, diuretics have been the most widely prescribed therapy for patients with essential hypertension. The cornerstone of antihypertensive therapy, thiazide diuretics have found acceptance as a first-step treatment in large-scale clinical trials.[1–3] As a result of the considerable clinical experience gained from these trials, diuretic dosages have substantially decreased. This has led to a reduction in both the incidence and severity of adverse reactions, especially the long-term effects on lipid and carbohydrate metabolism.[4–6] In addition, diuretics have reduced the morbidity and mortality associated with hypertension. The greatest benefits, however, have been the reduction in cerebrovascular accidents and complications secondary to cardiac or renal failure.[2,3] But disappointingly, the incidence of coronary heart disease has not decreased.

A potassium-sparing diuretic such as spironolactone, combined with a thiazide diuretic, is an effective way of reducing blood pressure (BP). Spironolactone is an aldosterone antagonist that reduces distal tubular potassium loss by competitive inhibition of aldosterone-dependent sodium/potassium exchange sites, and exerts its own antihypertensive action.[7–9]

Enalapril maleate, an angiotensin-converting enzyme (ACE) inhibitor, is also an effective antihypertensive agent. After oral administration, enalapril maleate is hydrolyzed into enalaprilate, the active metabolite that inhibits the enzyme responsible for the production of angiotensin II and the degradation of kinins. Inhibition of the ACE occurs within 2 to 4 hours and lasts for more than 24 hours, so that it can be administered in a single daily dose.[10] It has been shown that enalapril exerts its antihypertensive action in dose-dependent fashion up to 10 mg. A 20-mg dose is not markedly more effective than 10 mg, but has a longer duration of action.[11]

Although both spironolactone/altizide (S/A)—in a fixed-dose combination form—and enalapril act directly on the renin-angiotensin-aldosterone system, they do so at different points. This study was conducted to compare the respective safety and efficacy of these 2 antihypertensive agents in the treatment of moderate essential hypertension.

METHODS

Selection criteria and study design: The study consisted of 186 patients (108 men and 78 women), aged 19 to 80 years (mean 57.4 ± 12.3) with stable essential hypertension (diastolic BP between 100 and 120 mm Hg) as recorded on 2 consecutive visits before and after the

TABLE I Description of Patient Population

Parameter	S/A (n = 92)	Enalapril (n = 94)	p
Age (yr)	58.4 ± 12.1	56.5 ± 12.6	NS
Men	56%	61%	NS
Women	44%	39%	NS
Duration of hypertension	3.7 ± 4.3	2.8 ± 3.5	NS
Previous treatment	62%	56%	NS
DBP (mm Hg)			
Supine	107 ± 7	106 ± 6	NS
Standing	106 ± 8	106 ± 7	NS
Serum potassium (mmol/liter)	4.16 ± 0.31	4.19 ± 0.36	NS
Serum creatinine (μmol/liter)	95.8 ± 18.7	90.7 ± 19.6	NS
Natriuresis (mmol/24 hours)	129.6 ± 71.9	136.7 ± 83.7	NS

Values are expressed mean ± standard deviation.
DBP = diastolic blood pressure; NS = not significant; S/A = spironolactone + altizide.

placebo washout period. Patients with cardiac, cerebrovascular, renal or liver dysfunction were excluded from the study, as were patients with known hypersensitivity to either of the drugs, and pregnant or lactating women. All patients gave informed consent to participate in the study.

Study design and dosages: This was a randomized, multicenter, double-blind, parallel-group study with an 8-week treatment period preceded by a 4-week placebo washout phase. The patients were randomly assigned to 1 of the 2 treatment groups, either the S/A (15 mg/25 mg/day) group, or the enalapril (20 mg/day) group.

Clinical evaluation and laboratory values: Resting systolic and diastolic BP measurements were recorded after 5 minutes in the supine position and after 1 minute in the upright position. After 1 week of treatment, the patients were examined for possible signs of orthostatic hypotension, and clinical evaluations were performed after 4 and 8 weeks. Laboratory values were checked before and after the placebo run-in phase and after 4 and 8 weeks of treatment. Drug safety was assessed at each visit by recording any adverse reactions spontaneously brought up by the patient or elicited by direct questioning during the examination.

Statistical methods: The statistical analyses of the study results included the chi-square test, analysis of variance and calculation of correlation coefficients. Statistical significance was defined at the 5% level ($\alpha = 0.05$).

RESULTS

Table I, which summarizes the patient characteristics at the end of the placebo phase, shows that the 2 groups were comparable. Of the total 186 patients, 94 were assigned to the enalapril group and 92 to the S/A group. Forty percent of the patients in both groups had never been previously treated for hypertension, and the remaining patients had been treated for an average of 3.3 ± 3.9 years. No patients were lost to follow-up, but 4 in the S/A group and 5 in the enalapril group withdrew because of adverse reactions.

Blood pressure: After 8 weeks, significant and comparable decreases in BP were recorded with both regimens (Table II). In the S/A group, mean supine systolic and diastolic BP were significantly reduced (15 and 16%, respectively). BP decreased comparably in the enalapril group (13% systolic, 16% diastolic) (Fig. 1). By the end of the study, the percentage of patients with normalized BP (diastolic <95 mm Hg) was comparable for the 2 groups (71% S/A group, 73% enalapril group; p = 0.75). When the BP decreases were related to the age of the patients, a significant age-related effect was found (p = 0.03). Whereas enalapril produced a greater reduction in supine diastolic BP in patients younger than age 50 years (enalapril group, −19%; S/A group, −14%), BP in the patients older than 50 was more effectively controlled by S/A than by enalapril (−17 and −14%, respectively). Moreover, the decrease in supine diastolic BP in women, irrespective of age, appeared to be greater with S/A than with enalapril (−17 and −14%, respectively), although the difference was not statistically significant (Table III).

Laboratory values and adverse reactions: Laboratory values before and after treatment are listed in Table IV. Serum potassium levels changed somewhat in both groups (S/A group, −2%; enalapril group, +3%). There was 1 instance of hypokalemia in each group after the 8 weeks of treatment (serum potassium = 3.1 mmol/liter, S/A group; 3.3 mmol/liter, enalapril group). In addition, there were 2 cases of hyperkalemia in the enalapril group

TABLE II Mean Systolic and Diastolic Blood Pressure (mm Hg) Before and After Four and Eight Weeks of Treatment

	Spironolactone + Altizide				Enalapril			
	Before Treatment	After 4 Weeks	After 8 Weeks	%	Before Treatment	After 4 Weeks	After 8 Weeks	%
Systolic Blood Pressure								
Supine	181 ± 15*	158 ± 18†	154 ± 16†	−15†	176 ± 13*	155 ± 18†	152 ± 18†	−13†
Standing	178 ± 15*	154 ± 19†	153 ± 17†	−14†	173 ± 16*	151 ± 19†	147 ± 19†	−14†
Diastolic Blood Pressure								
Supine	107 ± 7	92 ± 10†	90 ± 9†	−16†	106 ± 6	91 ± 10†	89 ± 10†	−16†
Standing	106 ± 8	92 ± 11†	91 ± 11†	−14†	106 ± 7	90 ± 11†	89 ± 11†	−16†

* Significant difference (p <0.05) between 2 treatments.
† Significant difference (p <0.01) vs pretreatment value.
Values are expressed as mean ± standard deviation.

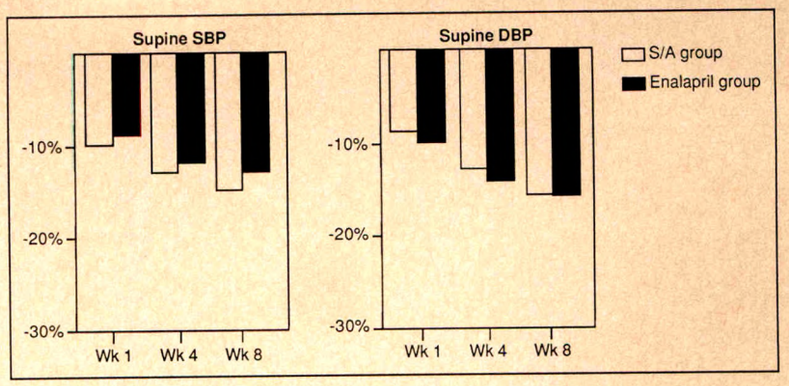


FIGURE 1. Relative variations in supine blood pressure after 1, 4 and 8 weeks of treatment. DBP = diastolic blood pressure; SBP = systolic blood pressure; S/A = spironolactone/altizide.

(5.3 and 5.4 mmol/liter). Serum creatinine increased moderately in both groups (+4%), and there were 2 cases of hypercreatininemia—1 in a patient from the S/A group (175 μmol/liter), and 1 in a patient from the enalapril group (185 μmol/liter). Although serum uric acid was significantly increased in the S/A group ($p < 0.01$), this did not result in any apparent clinical repercussions. All other laboratory values remained unchanged.

Adverse reactions (1 or more) were reported by 27 patients in the S/A group and by 32 in the enalapril group (Table V). These consisted mainly of gastrointestinal symptoms (5.4%) for the S/A group, and orthostatic hypotension (7.4%), dizziness (without confirmed hypotension, 6.4%), gastrointestinal symptoms (6.4%) and headache (5.3%) for the enalapril group. There was a difference (≥20 mm Hg) between supine and standing systolic BP in 6 patients in the S/A group and in 13 in the enalapril group. Adverse reactions leading to patient withdrawal from the study are listed in Table VI.

DISCUSSION

After 8 weeks of treatment, S/A and enalapril reduced BP to about the same extent (S/A group, supine systolic and diastolic BP, −15/−16%; enalapril group, supine systolic and diastolic BP −13/−16%) and in about the same percentage of patients (S/A, 71%; enalapril, 73%). The S/A combination proved more effective than enalapril in older patients (more than 50) and, in women, supine diastolic BP decreased more with the combination than with the ACE inhibitor regardless of age (Table VII). In contrast, supine diastolic BP was better con-

TABLE III Age-Related Relative Variations in Supine Diastolic Blood Pressure

	Age	
	≤ 50 Years (n = 39)	> 50 Years (n = 126)
S/A group (n = 78)	−14%	−17%
Enalapril group (n = 87)	−19%	−14%
Analysis of variance		
Age effect	p = 0.60	
Treatment effect	p = 0.43	
Age × treatment interaction	p = 0.03	

S/A = spironolactone/altizide.

TABLE IV Laboratory Values Before and After Eight Weeks of Treatment

Parameter	Spironolactone + Altizide		Enalapril	
	Before Treatment (n = 92)	After 8 Weeks (n = 85)	Before Treatment (n = 94)	After 8 Weeks (n = 88)
Serum				
Sodium (mmol/liter)	140.1 ± 2.3	139.6 ± 2.6	140.5 ± 2.7	140.0 ± 3.0
Potassium (mmol/liter)	4.16 ± 0.31	4.07 ± 0.36*,†	4.19 ± 0.36	4.28 ± 0.44*,†
Creatinine (μmol/liter)	95.8 ± 18.7	98.3 ± 20.6*	90.7 ± 19.6	93.9 ± 23.0*
Chloride (mmol/liter)	101.6 ± 3.5	100.6 ± 3.8*	101.5 ± 3.2	101.6 ± 3.7
Glucose (mmol/liter)	5.5 ± 0.9	5.5 ± 1.2	5.5 ± 1.0	5.3 ± 1.0
Cholesterol (mmol/liter)	5.8 ± 1.3	5.9 ± 1.1	5.9 ± 1.1	5.7 ± 1.2
Triglycerides (mmol/liter)	1.4 ± 0.6	1.5 ± 0.7*	1.6 ± 0.9	1.7 ± 1.0
Uric acid (μmol/liter)	327.9 ± 83.6	349.5 ± 108.7‡,§	320.2 ± 83.3	303.8 ± 79.9§
Urine				
Sodium (mmol/24 hours)	129.6 ± 71.9	156.9 ± 93.9‡	136.7 ± 83.7	135.9 ± 66.1*
Potassium (mmol/24 hours)	56.4 ± 21.6	68.9 ± 21.3‡,§	55.3 ± 21.0	60.3 ± 23.5*,§

* Significant difference ($p < 0.05$) vs pretreatment value.
† Significant difference ($p < 0.01$) between 2 treatments.
‡ Significant difference ($p < 0.01$) vs pretreatment value.
§ Significant difference ($p < 0.05$) between 2 treatments.
Values are expressed as mean ± standard deviation.

TABLE V Adverse Reactions

Reaction	Spironolactone + Altizide (n = 92) No.	%	Enalapril (n = 94) No.	%
Ageusia	0	—	1	1.1
Allergy (edema + cutaneous eruption)	2	2.2	0	—
Anorexia	0	—	1	1.1
Asthenia	3	3.3	4	4.3
Cutaneous reactions	1	1.1	1	1.1
Dizziness, vertigo, lipothymia	4	4.3	6	6.4
Gastrointestinal symptoms	5	5.4	6	6.4
Gynecomastia	0	—	0	—
Headache	4	4.3	5	5.3
Libidinal disturbances	1	1.1	1	1.1
Muscle cramps	2	2.2	2	2.1
Nervousness, anxiety	1	1.1	0	—
Orthostatic hypotension	3	3.3	7	7.4
Palpitations, tachycardia	3	3.3	4	4.3
Paresthesia, dysesthesia	2	2.2	1	1.1
Precordialgia	0	—	1	1.1
Sweating	1	1.1	0	—
Malaise	1	1.1	1	1.1
Total no. of reactions	33		41	

TABLE VI Adverse Reactions Leading to Withdrawal from the Study

Adverse Effects S/A Group* (n = 92)	Pts.	Adverse Effects Enalapril Group (n = 94)	Pts.
Headache, vertigo	1	Vagal malaise	1
Cutaneous eruption	1	Gastrointestinal intolerance	1
Asthenia	1	Vertigo	1
Gastrointestinal intolerance	1	Asthenia, gastrointestinal intolerance	1
		Dysesthesia in lower limbs	1

* Spironolactone/Altizide

TABLE VII Sex-Related Relative Variations in Supine Diastolic Blood Pressure

	Women (n = 67)	Men (n = 99)
S/A group (n = 79)	−17%	−16%
Enalapril group (n = 87)	−14%	−17%
Analysis of variance		
Sex effect	p = 0.59	
Treatment effect	p = 0.49	
Sex × treatment interaction	p = 0.11	

S/A = spironolactone/altizide.

trolled with enalapril than with the diuretics in patients younger than 50. The comparable results obtained with the 2 study drugs confirm previous results from a smaller clinical trial of 20 patients[12] and from 2 large, multicenter studies.[13,14]

Although evidence of the efficacy of diuretics in hypertension is overwhelming, their mechanism of action remains incompletely elucidated. In particular, the effectiveness of thiazides is only partially explained by their diuretic action. For example, the antihypertensive and natriuretic dose-effect curves are not the same; however, antihypertensive effects independent of sodium depletion have not been demonstrated. Similarly, efficacy of spironolactone cannot be solely explained by its diuretic (the natriuresis is modest) or hormonal action (hyperaldosteronism is not implicated in essential hypertension). In addition to the vasodilatory effect of spironolactone,[15] recent studies suggest that aldosterone antagonists exert a direct vascular action by modification of sodium influx in the arterial smooth muscle cells.[16] Moreover, the inhibition of slow calcium channels by spironolactone has been shown to occur at different receptor sites from those of dihydropyridine and phenylalkylamine.[17]

In this study, the variations in biologic parameters, such as serum creatinine, serum potassium, blood glucose or lipid values, were comparable for S/A and enalapril. The increase in urinary excretion of uric acid usually found with diuretics, except for spironolactone,[7,18,19] remained moderate, and clinically insignificant. The incidence of adverse reactions was similar for the 2 antihypertensive agents used in this study.

In conclusion, the S/A fixed-dose combination and enalapril were found to be equally safe and effective in the treatment of moderate hypertension. The long clinical experience with spironolactone and altizide and their proven ability to reduce long-term cerebrovascular complications make them the drug of choice for initial therapy of mild to moderate hypertension without renal involvement, especially in patients older than 50.

REFERENCES

1. Amery A, Birkenhager W, Brixko P, Bulpitt C, Clement D, Deruyttere M, DeSchaepdryver A, Dollery C, Fagard R, Forette F, Forte J, Hamdy R, Henry JF, Joossens JV, Leonetti G, Lund-Johansen P, O'Malley K, Petrie J, Strasser T, Tuomilehto J, Williams B. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. *Lancet 1985;1:1349–1354.*

2. (The) IPPPSH Collaborative Group: Cardiovascular and risk factors in a randomized trial of treatment based on the beta-blocker oxprenolol: the International Prospective Primary Prevention Study in Hypertension. *J Hypertens 1985;3:379–392.*

3. Medical Research Council Working Party: MRC trial of treatment of mild hypertension: Principal results. *Br Med J 1985;291:97–104.*

4. Berglund G, Andersson O. Beta-blockers or diuretics in hypertension? A six year follow-up of blood pressure and metabolic side effects. *Lancet 1981;1:744–747.*

5. Helgeland A. Treatment of mild hypertension: a five year controlled drug trial. The Oslo study. *Am J Med 1980;69:725–732.*

6. Veterans Administration Cooperative Study Group on Antihypertensive Agents: propranolol or hydrochlorothiazide alone for the initial treatment of hypertension: effect on plasma glucose and glucose tolerance. *Hypertension 1985;7:1008–1016.*

7. Corvol P, Menard J. Spironolactones. *Sem Hôp Paris 1987;63:1535–1542.*

8. Jeunemaître X, Chatellier G, Kreft-Jais C, Charru A, Devries C, Plouin P-F, Corvol P, Menard J. Efficacy and tolerance of spironolactone in essential hypertension. *Am J Cardiol 1987;60:820–825.*

9. Scherstén B, Thulin T, Kuylenstierna J, Eugström M, Karlberg BE, Tolagen K, Nordlander S, Nilsson G. Clinical and biochemical effects of spironolactone administered once daily in primary hypertension: Multicenter Sweden Study. *Hypertension 1980;2:672–679.*

10. Galezowski N. L'énalapril: un nouvel inhibiteur de l'enzyme de conversion de l'angiotensine dans le traitement de l'hypertension artérielle. *Information Cardiol 1984;October:861–865.*

11. Gavras H, Biollaz J, Waeber B, Brunner HR, Gavras I, Davies RO. Antihypertensive effect of the new oral angiotensin converting enzyme inhibitor "MK-421." *Lancet 1981;2:543–546.*

12. Gibelin P, Durand Ph, Baudouy M, Camous J-P, Morand Ph. Efficacité et

tolérance de l'énalapril comparées à celles de l'altizide associée à la spironolactone chez des patients atteints d'hypertension artérielle modérée. *Ann Cardiol Angeiol 1986;35:279–283.*

13. Helgeland A, Strommen R, Hagelund CH, Tretli S. Enalapril, atenolol, and hydrochlorothiazide in mild to moderate hypertension: a comparative multicenter study in general practice in Norway. *Lancet 1986;1:872–875.*

14. Vidt DG. A controlled multiclinic study to compare the antihypertensive effect of MK-421, hydrochlorothiazide, and MK-421 combined with hydrochlorothiazide in patients with mild to moderate essential hypertension. *J Hypertens 1984;2:suppl 2:81–88.*

15. Meyer-Heine A, Ansquer JC, Hayoun C, Lagrue G. Le mécanisme d'action d'un hypotenseur étudié par l'analyse du carotidogramme. Application aux antialdostérones. *Therapie 1981;36:623–630.*

16. Moura A-M, Angeli M, Worcel M. Extrarenal effects of aldosterone and antimineralocorticoid compounds: mechanism of action on arterial smooth muscle. *Kidney Int 1988;34:S8–S11.*

17. Dacquet C, Loirand G, Mironneau C, Mironneau J, Pacaud P. Spironolactone inhibition of contraction and calcium channels in rat portal vein. *Br J Pharmacol 1987;92:535–544.*

18. Crane MG, Harris JJ. Effect of spironolactone in hypertensive patients. *Am J Med Sci 1970;260:311–330.*

19. Lawrie TDV, Lorimer AR, Jones RW, Kidner PH, James IM, Cummin P, Joy MD, Kubik MM, Bennet PN, Lewis LD. Spironolactone and propranolol in the management of idiopathic hypertension. *Acta Ther 1984;10:257–270.*

Spironolactone and Altizide Used in Combination with Enalapril: Twenty-Four-Hour Ambulatory Recording of Blood Pressure

Pascal Poncelet, MD, Marie Wehrlen, MD, Bruno Pelletier, MD, and Michel-Hubert Capron, MD

The addition of enalapril or acebutolol to a regimen of altizide + spironolactone in patients with moderate hypotension was investigated in a multicenter study of 53 patients. The patients underwent semiambulatory 24-hour blood pressure monitoring, especially to observe hypotensive episodes. In the 25 patients uncontrolled with altizide + spironolactone alone, enalapril and acebutolol were about equally effective in reducing blood pressure. The incidence of hypotension was low and comparable for both treatment groups, provided that the initial dose of angiotensin-converting enzyme inhibitor was low (5 mg).

(Am J Cardiol 1990;65:33K–35K)

From the Cardiology Department, Darcy Hospital, Henin-Beaumont; and Laboratories Searle, 92 Boulogne Billancourt, France.

Address for reprints: Pascal Poncelet, MD, Clinique Medico-Chirurgicale Darcy, rue Philibert Robiaud, 62110 Henin-Beaumont, France.

Diuretics are the most frequently prescribed antihypertensive drugs because they are considered safe, effective and well tolerated.[1,2] However, they may not by themselves suffice to control hypertension, at which time they are often used in combination with other drugs, such as angiotensin-converting enzyme (ACE) inhibitors. The antihypertensive effects of thiazide or loop diuretics are to some extent blunted by the diuretic-induced stimulation of the renin-angiotensin-aldosterone system,[3,4] resulting in increased renin secretion. ACE inhibitors block this mechanism, and thus potentiate the antihypertensive effect. This can result in significant hypotension.[5] On the other hand, the combination of β blockers and diuretics is known to be both safe and effective.[6] This study was performed to compare the safety and efficacy (with emphasis on hypotension) of the addition of an ACE inhibitor (enalapril) or a β blocker (acebutolol) to a therapeutic regimen consisting of altizide and spironolactone (A/S).

METHODS

A randomized, open, multicenter study was performed to investigate the hypotensive action of the addition of enalapril (5, 10 and 20 mg) or acebutolol (400 mg) to a regimen consisting of A/S in patients with moderate hypertension. This was investigated using 24-hour ambulatory blood pressure (BP) monitoring.

Fifty-three hypertensive patients (95 mm Hg [diastolic BP $\leq$120 mm Hg] and 160 mm Hg systolic BP [$\leq$190 mm Hg]) were treated for 4 weeks with A/S (1 tablet per day, 15 mg altizide + 25 mg spironolactone). BP was normalized in 23 of the 53 patients (diastolic BP $\leq$90 mm Hg and systolic BP $<$160 mm Hg) at the end of the 4 weeks (Table I). In this group, supine BP decreased from 173 $\pm$ 15 mm Hg (systolic) and 100 $\pm$ 11 mm Hg (diastolic) to 143 $\pm$ 16 and 86 $\pm$ 8 mm Hg, respectively.

Semiambulatory (Bard-Sentron™) 24-hour BP monitoring was continued in patients whose BP was inadequately controlled (n = 25). After 1 week of monitoring, patients were randomly assigned to the different treatment groups: A/S + enalapril 20 mg (n = 7); A/S + enalapril 10 mg (n = 7); A/S + enalapril 5 mg (n = 5); or A/S + acebutolol 400 mg (n = 6). BP monitoring was continued.

These 25 patients consisted of 6 men and 19 women, average age 50 $\pm$ 11 years. Mean supine BP was 180 $\pm$ 14 mm Hg (systolic) and 106 $\pm$ 9 mm Hg (diastolic).

TABLE I Blood Pressure Values Before and After Treatment with A/S in Patients Controlled by the A/S Combination (n = 23)

	Treatment	
	Before (mm Hg)	After 4 Weeks (mm Hg)
Supine		
SBP	173 ± 15	143 ± 16
DBP	100 ± 11	86 ± 8
Upright		
SBP	170 ± 13	142 ± 18
DBP	101 ± 11	85 ± 9

Values are expressed as mean ± standard deviation.
A/S = altizide + spironolactone; DBP = diastolic blood pressure; SBP = systolic blood pressure.

TABLE II Demographic and Clinical Parameters of Patients (n = 25) in the Two (Enalapril and Acebutolol) Treatment Groups

Men	6 (24%)
Women	19 (76%)
Age (yr)	49.9 ± 10.8%
Weight (kg)	70 ± 14
SBP, supine (mm Hg)	180 ± 14
SBP, upright (mm Hg)	183 ± 16
DBP, supine (mm Hg)	106 ± 14
DBP, upright (mm Hg)	108 ± 9

Values are expressed as mean ± standard deviation.
DBP = diastolic blood pressure; SBP = systolic blood pressure.

TABLE III Biochemical Parameters for the Two Treatment Groups (n = 25)

Parameter	Value
Serum creatinine (μmol/liter)	80.7 ± 18.0
Serum sodium (mmol/liter)	141 ± 2
Serum potassium (mmol/liter)	4.0 ± 0.5
Serum glucose (mmol/liter)	5.8 ± 1.2
Serum uric acid (μmol/liter)	325 ± 85
Serum protein (g/liter)	73 ± 5
Hematocrit (%)	44 ± 4
Urine sodium concentration (mmol/liter)	94 ± 49
Plasma renin activity (ng/ml/hour)	1.63 ± 1.74

Mean serum creatinine was 81 ± 18 μmol/liter, mean natriuresis every 24 hours was 94 ± 49 mmol/liter, and mean plasma renin activity was 1.6 ± 1.7 ng/ml/hour (Tables II and III).

RESULTS

With enalapril or acebutolol, mean BP over 24 hours decreased significantly ($p < 0.001$) and in comparable fashion for the 2 drugs (enalapril, −15 ± 0.10% systolic, −12 ± 0.10% diastolic; acebutolol, −11 ± 0.07% systolic, −8 ± 0.10% diastolic) (Fig. 1, Table IV).

The 2 treatment groups were comparable in terms of incidence of hypotensive episodes per 24 hours during the period they were treated with A/S alone. Hypotension, as recorded by 24-hour BP monitoring, was defined as a

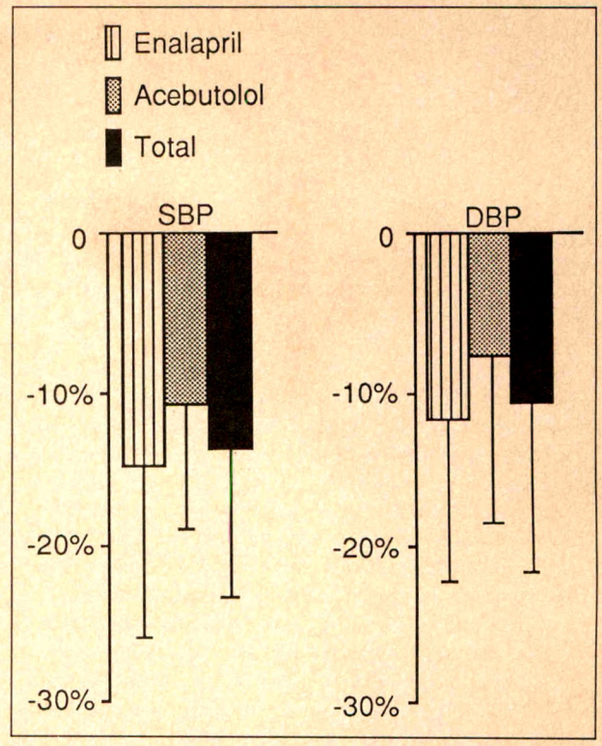


FIGURE 1. Relative variations in mean blood pressure over 24 hours before and after treatment with enalapril and altizide/spironolactone or acebutolol + altizide/spironolactone. A significant decrease occurred in blood pressure after the addition of enalapril or acebutolol ($p < 0.001$). No significant difference was seen between the 2 treatment regimens. DBP = diastolic blood pressure; SBP = systolic blood pressure.

TABLE IV Relative Variations in Mean Blood Pressure Over 24 Hours Before and After Treatment

	Enalapril Group (n = 19)	Acebutolol Group (n = 6)	Total (n = 25)
SBP	−0.15 ± 0.10	−0.11 ± 0.07	−0.14 ± 0.09*
DBP	−0.12 ± 0.10	−0.08 ± 0.10	−0.11 ± 0.10*

* Significant difference between values ($p < 0.001$) before and after treatment. No significant difference between the 2 treatment groups.
DBP = diastolic blood pressure; SBP = systolic blood pressure.

TABLE V Difference (Δ) Between the Number of Hypotensive Episodes Occurring with the Enalapril and Acebutolol Treatment Groups Versus the Altizide/Spironolactone (A/S) Group

Δ	E Group (n = 19)	A Group (n = 6)	p_1	p_2
Over 24 hours*	+0.5 ± 2.5	+0.5 ± 2.4	NS	NS
From 0 to 6 hours*	+0.3 ± 0.9	−0.3 ± 0.8	0.13	NS
From 6 to 12 hours*	−0.3 ± 1.1	+0.3 ± 1.2	NS	NS
From 12 to 18 hours*	+0.4 ± 1.1	+0.5 ± 1.2	NS	0.05
From 18 to 24 hours*	0 ± 0.7	0 ± 0.6	NS	NS

* After dosing.
A = acebutolol; E = enalapril; NS = not significant; p_1 = difference between enalapril and acebutolol groups; p_2 = difference between enalapril or acebutolol + A/S (together) and A/S alone.

decrease of at least 15% in systolic or diastolic BP vs the previous value. Once enalapril and acebutolol were added, the incidence of hypotension continued to be similar with all therapeutic regimens, but the 24-hour distribution varied slightly (Table V). There were more hypotensive episodes in the 12 PM to 6 PM period in the groups treated with A/S + enalapril or acebutolol ($p = 0.05$) than in the group treated with A/S alone. In addition, in the first 6 hours after dosing, hypotensive episodes appeared to be more frequent in the enalapril ($+0.3 \pm 0.9$) than in the acebutolol group (-0.3 ± 0.8) ($p = 0.13$). Clinically, 3 patients had symptoms of hypotension. One was receiving enalapril, 20 mg, and the other two, 10 mg enalapril + A/S. The mean change in plasma renin activity before treatment and after 5 weeks of treatment with A/S was +3.2 ng/ml/hour in the 3 patients experiencing clinical hypotension vs +1.9 ng/ml/hour in the other patients. Hypotensive episodes were apparent on the 24-hour BP recording in 1 patient in 3.

CONCLUSION

Overall, the addition of enalapril or acebutolol to an A/S regimen was well tolerated and did not increase the incidence of episodes of hypotension. Thus, addition of an ACE inhibitor such as enalapril is an alternative for patients who do not respond sufficiently to altizide + spironolactone, although, because of the potential for sodium depletion, it would be prudent to keep the dose of the ACE inhibitor low (5 mg), especially during drug initiation.

REFERENCES

1. Hollifield JW. Thiazide treatment of hypertension. *Am J Med 1986;80:suppl 4A:8–12.*

2. The 1984 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med 1984;144:1045–1057.*

3. Dyckner T, Wester PO. Diuretic treatment and magnesium losses in electrolytes and cardiac arrhythmias. *London: Royal Society of Medicine International Symposium Series, 1981:145–152.*

4. Shoback DM, Williams GH. Potassium-sparing diurectics: clinical pharmacology and therapeutic uses. *Drug Therapy 1982;12:113–121.*

5. Hodsman GP, Johnston CI. Angiotensin converting enzyme inhibitors: drug interactions. *J Hypertens 1987;5:1–6.*

6. Rudd P, Blaschke TF. Antihypertensive agents and the drug therapy of hypertension. In: Gilman A, Goodman LS, Rall TW, Murad F, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 7th ed. *New York: Macmillan, 1985:784–805.*

Spironolactone Versus Nifedipine in Essential Hypertension

Michel Henry, MD, Marie Wehrlen, MD, Bruno Pelletier, MD, and Michel-Hubert Capron, MD

In a double-blind, randomized, multicenter study of 194 patients with moderate hypertension, spironolactone and nifedipine were found to reduce blood pressure (BP) to about the same extent and in the same percentage of patients after 45 days of treatment (47 and 50%, respectively). At that point, the patients controlled by either drug continued on their regimen for another 45 days, while patients whose BP was still elevated (diastolic BP >90 mm Hg), received the other drug in addition. After 45 days of combination therapy, 63% of the patients had normal BP, whereas those receiving monotherapy largely remained normotensive (96% in the spironolactone group and 88% in the nifedipine group). The adverse effects were not severe with either group, but the incidence was markedly higher in the nifedipine group.

(Am J Cardiol 1990;65:36K–38K)

From the Department of Cardiology, Polyclinic, Essey-les-Nancy, and Laboratories Searle, 92 Boulogne-Billancourt, France.

Address for reprints: Michel Henry, MD, Clinique d'Essey, 7, rue Parmentier, 54311 Essey-les-Nancy, France.

The antihypertensive effect of spironolactone, used alone or in combination, has been amply demonstrated.[1–3] A review of published reports of the last 20 years shows that spironolactone is especially effective when hypertension is associated with low renin levels, and when the elevated blood pressure (BP) is specifically responsive to aldosterone antagonists.[4,5] Spironolactone is often used in combination with other diuretics, especially thiazides,[3,4,6] or with other types of antihypertensive agents with good results.[7] This study was conducted to (1) compare the safety and antihypertensive effectiveness of a potassium-sparing diuretic such as spironolactone with that of a calcium channel blocker (nifedipine), and (2) evaluate the safety and efficacy of the 2 drugs used in combination.

METHODS

A double-blind, randomized, multicenter study was conducted over a 90-day period to evaluate the safety and efficacy of spironolactone and sustained-release nifedipine in 184 patients with moderate essential hypertension (165 mm Hg [≤200] systolic and 100 mm Hg [≤120] diastolic BP). Characteristics of the 2 patient groups are summarized in Table I. The study was preceded by a 4-week washout period, after which the patients (92 in each group) were treated with either spironolactone (75 mg/day) or sustained-release nifedipine (40 mg twice daily). At the end of 45 days of monotherapy either spironolactone or nifedipine was added to the treatment for those patients whose BP remained elevated. The effectiveness of the monotherapy and the combination treatment was evaluated again after another 45 days (90 days total).

RESULTS

After 45 days of single-drug treatment, BP remained elevated (diastolic BP >90 mm Hg) in 72 patients; they then began therapy with the other drug in addition to the one they were already taking. At day 45, the decrease in BP and the percentage of patients whose BP had normalized with the single drug (diastolic BP ≤90 mm Hg) were comparable for the 2 drugs (47% in the spironolactone group, 50% in the nifedipine group) (Table II). At the 90-day follow-up, the patients (96% of the spironolactone group and 88% in the nifedipine group) had maintained their lower pressures.

Of the 72 patients who required concomitant treatment with spironolactone or nifedipine, BP in 63% reached normal levels after 45 days of combination therapy (Fig. 1, Tables II and III).

TABLE I Characteristics of Patient Groups

	Spironolactone Group (n = 85)	Nifedipine Group (n = 77)	Total (n = 162)	p
Age (yr)	60 ± 10	58 ± 11	59 ± 10	NS
Men	55%	56%	55%	NS
Women	45%	44%	44%	
Duration of hypertension (yr)	3 ± 4.5	4 ± 4	3.6 ± 4	NS
Height/weight	2 ± 0.3	2 ± 0.3	2 ± 0.3	NS
Sup SBP (mm Hg)	177 ± 10	178 ± 11	178 ± 10	NS
Sup DBP (mm Hg)	105 ± 5	106 ± 6	106 ± 5.5	NS
Std SBP (mm Hg)	175 ± 9	176 ± 10	176 ± 9	NS
Std DBP (mm Hg)	105 ± 5	106 ± 6	106 ± 5.5	NS
Serum potassium (mmol/liter)	4.27 ± 0.36	4.22 ± 0.35	4.24 ± 0.35	NS
Serum creatinine (μmol/liter)	91.2 ± 18.3	91.5 ± 20.7	91.4 ± 19.5	NS

DBP = diastolic blood pressure; NS = not significant; SBP = systolic blood pressure; std = standing; sup = supine.

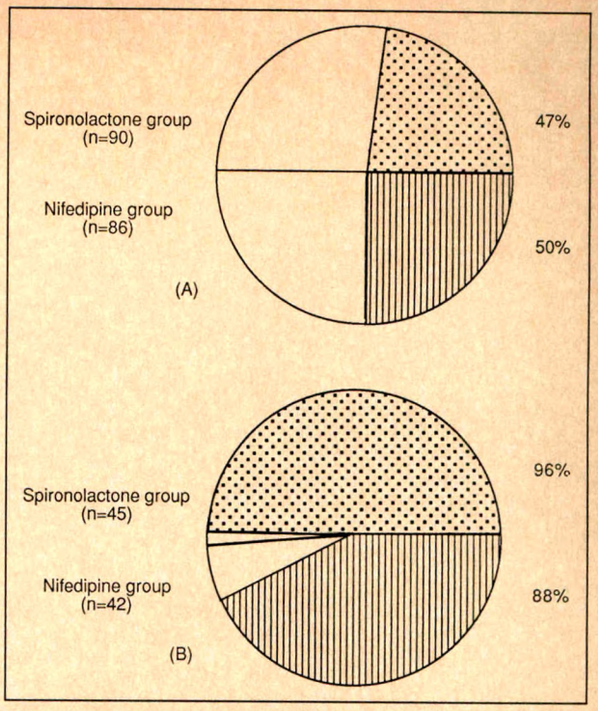


FIGURE 1. Percent of patients with blood pressure (BP) normalized (supine diastolic BP ≤90 mm Hg) with spironolactone or nifedipine alone (monotherapy). (*A*), percent with normal BP at day 45; (*B*), percent with reduced BP at day 45 and still normal at day 90.

Laboratory values: Serum potassium varied only minimally in the spironolactone group (+0.2 mmol/liter). Plasma glucose was slightly increased in both groups (+0.2 mmol/liter). Serum creatinine did not change (Table IV).

Adverse effects: Adverse effects (1 or more) were recorded in 15% of the patients in the spironolactone group and in 47% of patients in the nifedipine group. In the nifedipine group these consisted chiefly of flushing or heat sensation (22%), peripheral edema (20%), erythema (8%) and headache (7%), whereas in the spironolactone group gastrointestinal distress was experienced by 4%. In the patients receiving both nifedipine and spironolactone, 1 or more adverse effects were recorded in 21%. The most frequent were peripheral edema (11%) and erythema (6%) (Table V). Three patients in the spironolactone group and 10 in the nifedipine group withdrew from the study because of untoward effects. In addition, 12 patients were absent for the control visits of day 45 or day 90, but not lost at follow-up. The patients who withdrew because of adverse effects were counted as treatment failures in the analysis of the results.

CONCLUSIONS

After 6 weeks of treatment, spironolactone (75 mg/day) and sustained-release nifedipine (40 mg twice daily)

TABLE II Blood Pressure Before and After Monotherapy with Spironolactone or Nifedipine

	Spironolactone			Sustained-Release Nifedipine		
	Baseline (n = 92)	Day 45 (n = 85)	Day 90 (n = 45)	Baseline (n = 92)	Day 45 (n = 77)	Day 90 (n = 42)
SBP (sup)	177 ± 10	160 ± 17*	144 ± 13*	178 ± 11	158 ± 16*	150 ± 10*
SBP (std)	175 ± 9	157 ± 18*	142 ± 14*	176 ± 10	155 ± 16*	146 ± 7*
DBP (sup)	106 ± 5	93 ± 10*	84 ± 6*	106 ± 6	91 ± 10*	86 ± 6*
DBP (std)	105 ± 5	93 ± 10*	85 ± 6*	106 ± 6	92 ± 11*	86 ± 6*

* Significant difference vs baseline ($p < 0.001$).
Abbreviations as in Table I.
Values are expressed as mean ± standard deviation.

TABLE III Changes in Blood Pressure After 45 Days of Combination Therapy with Spironolactone + Nifedipine

	SBP (sup)	DBP (sup)	SBP (std)	DBP (std)
Spironolactone + nifedipine (n = 72)	−0.08 ± 0.07*	−0.10 ± 0.09*	−0.09 ± 0.08*	−0.11 ± 0.09*

* Significant difference vs control blood pressure value before initiation of combination therapy ($p < 0.001$).
Abbreviations as in Table I.

TABLE IV Laboratory Values Before and After Treatment with Spironolactone or Nifedipine

	Spironolactone		Sustained-Release Nifedipine	
	Baseline (n = 92)	Day 45 (n = 85)	Baseline (n = 92)	Day 45 (n = 77)
Serum sodium (mmol/liter)	140 ± 3	140 ± 2*†	141 ± 2	141 ± 2*
Serum potassium (mmol/liter)	4.2 ± 0.4	4.5 ± 0.4*†	4.2 ± 0.4	4.2 ± 0.4*
Serum chloride (mmol/liter)	102 ± 3	102 ± 3*	103 ± 3	103 ± 3*
Plasma glucose (mmol/liter)	5.5 ± 0.8	5.7 ± 1.3†	5.4 ± 0.7	5.6 ± 0.7†
Serum cholesterol (mmol/liter)	5.9 ± 1.1	6.0 ± 1.0	6.1 ± 1.2	6.0 ± 1.1
Serum triglycerides (mmol/liter)	1.47 ± 0.83	1.50 ± 0.84	1.44 ± 0.69	1.51 ± 0.76†
Serum uric acid (μmol/liter)	316 ± 96	318 ± 92*†	312 ± 87	293 ± 78*†
Serum creatinine (μmol/liter)	92.6 ± 17.5	92.3 ± 17.3†	91.2 ± 20.0	90.6 ± 20.3

* Significant difference between the 2 drugs ($p < 0.05$).
† Significant difference vs before treatment ($p < 0.05$).
Values are expressed as mean ± standard deviation.

TABLE V Adverse Effects

	Nifedipine Group (n = 92)		Spironolactone Group (n = 92)		Spironolactone + Nifedipine Group (n = 72)	
	No.	% Group	No.	% Group	No.	% Group
Tinnitus	2	2	0	0	0	0
Weakness	2	2	1	1	2	3
Dry mouth	2	2	0	0	0	0
Flushing, heat sensation	20	22	0	0	1	1
Headache	6	7	0	0	0	0
Erythema	7	8	1	1	4	6
GI distress	2	2	4	4	0	0
Syncope	2	2	0	0	0	0
Nausea	1	1	2	2	0	0
Peripheral edema	18	20	1	1	8	11
Tachycardia	2	2	0	0	1	1
Tremor	2	2	0	0	0	0
Dizziness	2	2	1	1	1	1
Other	9	10	6	7	3	4
Total	77		16		20	

GI = gastrointestinal.

were found to have comparable efficacy, both in terms of antihypertensive action and in the number of patients achieving controlled BP. Concomitant treatment (spironolactone + nifedipine) normalized BP in 63% of patients whose BP could not be controlled with either agent alone; however, the incidence of undesirable side effects was markedly higher with sustained-release nifedipine than with spironolactone.

REFERENCES

1. Corvol P, Menard J. Spironolactones. *Sem Hôp Paris 1987;63:1535–1542.*

2. Johnston LC, Grieble HG. Treatment of arterial hypertensive diseases with diuretics: spironolactone, an aldosterone antagonist. *Arch Intern Med 1967; 119:225–238.*

3. Winer BM, Lubbe WF, Colton T. Antihypertensive action of diuretics: comparative study of aldosterone antagonist and a thiazide, alone and together. *JAMA 1968;204:117–121.*

4. Adlin EV, Marks AD, Channick BJ. Spironolactone and hydrochlorothiazide in essential hypertension. Blood pressure response and plasma renin activity. *Arch Intern Med 1972;130:855–858.*

5. Vaughan ED Jr, Laragh JH, Gavras I. Volume factor in low and normal renin essential hypertension. Treatment with either spironolactone or chlorthalidone. *Am J Cardiol 1973;32:523.*

6. Dueymes JM, Eche JP, Bellanger B. Etude coopérative de l'efficacité et de la tolérance de l'Aldactazine en monothérapie dans l'hypertension artérielle essentielle modérée. *Medecine Cardio-Vasculaire:60 (supplement to Quotidien du Medecin):January 31, 1986;1–7.*

7. Scholn D, Wehrlen M, Petit T, Spiesser R, Assyag P, Pelletier B, Capron MH. Efficacité et tolérance de l'association Aldactazine®-captopril dans l'hypertension artérielle essentielle légère à modérée. *Gazette Medicale 1987;94:1-8.*

Editorial Overview

Alain Castaigne, MD

The introduction of potent diuretics in the treatment of congestive heart failure caused a significant change in the clinical course of this disease.[1] Subsequent clinical trials have been aimed at the evaluation of new therapeutic approaches to the treatment of cardiac failure—in particular the evaluation of combination therapy: diuretics alone vs diuretics combined with newer therapy. This is particularly the case with vasodilators.[2,3] The question is not whether there is another first-line drug for the treatment of heart failure[4] but rather which drug should be added to the diuretic therapy.[5]

Some perspective on therapy with diuretics comes from their use in treating hypertension. In the treatment of hypertension, it has been shown repeatedly that antihypertensive regimens using diuretics as a first step are effective in reducing total mortality, stroke and congestive heart failure.[6,7] The Hypertension Detection and Follow-up Program showed that better control of blood pressure reduced not only total mortality but also mortality due to cardiovascular diseases and stroke.[8,9] In the study, the special intervention group received diuretics as the first-step drug. An impressive regression of left ventricular hypertrophy was observed.[10] Currently, only diuretics reduce total mortality and left ventricular hypertrophy (the 2 main objectives of antihypertensive treatment).

The main concern when using loop and thiazide diuretics is potassium and magnesium depletion.[11] This effect is linked to the stimulation of the renin-angiotensin-aldosterone system.[12] Activation occurs during the treatment of essential hypertension by thiazide diuretics but is much more pronounced in patients with heart failure[13] where the renin-aldosterone system is activated as part of the neuroendocrine adaptation to low cardiac output.[14] The introduction of loop or thiazide diuretics induces or increases the activation of the renin-angiotensin-aldosterone system, resulting in a decrease in plasma potassium and magnesium.[15] Hypokalemia and hypomagnesemia can be corrected most effectively by using antialdosterone compounds.[16]

Spironolactone is the prototype of a unique class of pharmacologic agents that act purely as competitive inhibitors of aldosterone and, in our opinion, must be a part of any diuretic treatment program. It may be used as first-line treatment,[17] or as a part of combined diuretic regimens with thiazides or furosemide in hypertension or congestive heart failure.

From the Cardiology Department, Hôpital Henri Mondor, Créteil, France.

Address for reprints: Alain Castaigne, MD, Cardiology Department, Hôpital Henri Mondor, 94010 Créteil, France.

Diuretics decrease elevated blood pressure and relieve the symptoms of dyspnea and edema in congestive heart failure. They may also slow the progression of congestive heart failure. In hypertension, diuretics reduce the incidence of overt heart failure[6,7] and induce a regression of left ventricular hypertrophy[10]—the main sign of left ventricular dysfunction resulting from hypertension.

In congestive heart failure, blood pressure is often said to be "normal," but according to Laplace's Law, normal blood pressure in the presence of a dilated left ventricle must result in an increase in systolic wall tension. Thus, even "normal" blood pressure may in fact be too high[18] and is maintained by the activation of the noradrenergic and renin-angiotensin-aldosterone systems[18] and by chronic sodium retention which increases vascular stiffness.[19] Diuretics, by reducing blood pressure and preventing sodium retention, decrease left ventricular pre- and afterload and may slow the progression of left ventricular failure.

Diuretics should therefore remain a first choice in the treatment of hypertension and heart failure. Using spironolactone alone or in combination with a thiazide or furosemide avoids the main unwanted effect of these agents—hypokalemia and hypomagnesemia—and it is for this reason that this drug is so widely used in many countries. It has been the leading diuretic in Japan and France for several years.

REFERENCES

1. Packer M. How should we judge the efficacy of drug therapy in patients with chronic congestive heart failure: the insights of six blind men. *J Am Coll Cardiol 1987;9:433–440.*

2. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH, Goldman S, Cobb FR, Shah PM, Saunders R, Fletcher RD, Loeb HS, Hughes VC, Baker B. Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a veterans administration cooperative study (V-HeFT) *N Engl J Med 1986;314:1547–1553.*

3. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med 1987;316:1429–1435.*

4. Katz AM. Changing strategies in the management of heart failure. *J Am Coll Cardiol 1989;13:513–523.*

5. Parmley WW, Smith TW, Pitt B. Should digoxin be the drug of first choice after diuretics in chronic congestive heart failure? *J Am Coll Cardiol 1988; 12:265–273.*

6. Veterans Administration Cooperative Study Group on Anti-Hypertensive Agents. Effects of treatment on morbidity in hypertension: results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. *JAMA 1967;202: 1028–1034.*

7. Veterans Administration Cooperative Study Group on Anti-Hypertensive Agents. Effects of treatment on morbidity in hypertension: results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *JAMA 1970;213: 1143–1152.*

8. Hypertension Detection and Follow-Up Program Cooperative Group. The effect of treatment on mortality in mild hypertension. *N Engl J Med 1982; 307:976–980.*

9. HDFP Cooperative Group. Persistence of reduction in blood pressure and mortality of participants in the Hypertension Detection and Follow-up Program. *JAMA 1988;259:2113–2122.*

10. HDFP Cooperative Group. Five year findings of the HDFP: prevention and reversal of left ventricular hypertrophy with anti-hypertensive drug therapy. *Hypertension 1985;7:105–112.*
11. Papademetriou V, Fletcher R, Kharti IM, Freis ED. Diuretic-induced hypokalemia in uncomplicated systemic hypertension: effect of plasma potassium correction on cardiac arrhythmias. *Am J Cardiol 1983;52:1017–1022.*
12. Laragh JH. Spironolactone for treatment of hypertension or congestive heart failure: a review. *Excerpta Medica 1987:1–28.*
13. Knight RK, Miall PA, Hawkins LA, Dacombe J, Edwards CR, Hamer J: Relation of plasma aldosterone to diuretic treatment in patients with severe heart disease. *Br Heart J 1979;42:316–325.*
14. Dzau VJ, Colucci WS, Hollenberg NK, Williams GH. Relationship of the renin-angiotensin-aldosterone system to clinical state in congestive heart failure. *Circulation 1981;63:645–651.*
15. Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P. Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. *Br Heart J 1987;57:17–22.*
16. Jackson PR, Ramsay LE, Wakefield V. Relative potency of spironolactone, triamterene, and potassium chloride in thiazide-induced hypokalemia. *Br J Clin Pharmacol 1982;14:257–263.*
17. Corvol P, Menard J, Milliez P. Place des anti-aldostérones dans le traitement de l'hypertension artérielle. *Rev Prat 1973;23:671–681.*
18. Harris P. Congestive cardiac failure: central role of the arterial blood pressure. *Br Heart J 1987;58:190–203.*
19. Zelis R, Lee G, Mason DT. Influence of experimental edema on metabolically determined blood flow. *Circ Res 1974;34:482–490.*

Short- and Long-Term Mechanisms of Sudden Cardiac Death in Congestive Heart Failure

Richard H. Helfant, MD

This report presents an overview of the problem of treating congestive heart failure. Emphasis is on the arrhythmia component and the complex interrelationships of critical electrolytes and pathophysiologic factors that can lead to sudden cardiac death.
(Am J Cardiol 1990;65:41K–43K)

From Cedars-Sinai Medical Center, and UCLA School of Medicine, Los Angeles, California.

Address for reprints: Richard H. Helfant, MD, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Los Angeles, California 90048.

The magnitude of the problem of severe ventricular arrhythmia and sudden cardiac death in patients with congestive heart failure (CHF) is compelling because of the high percentage of sudden unexpected deaths. Studies using 24-hour ambulatory monitoring indicate that 60 to 90% of patients with CHF have frequent or complex ventricular ectopy; approximately 40 to 60% have nonsustained ventricular tachycardia.[1] In addition, 33 to 45% of all deaths in patients with CHF are sudden and unexpected, and more recent estimates approach 50%. Thus, the frequency of sudden unexpected death is greater in patients with CHF than in any other definable subset of patients in cardiovascular medicine.

When sufficient myocardial damage is sustained to cause a decreased cardiac output, several compensatory mechanisms become activated. They may include an increase in sympathetic activity, and an increased activation of the renin-angiotensin-aldosterone system. Once activated, the compensatory mechanisms can then lead to excessive vasoconstriction and retention of sodium and water. In addition, several of these compensatory mechanisms may induce changes in intracellular and extracellular electrolytes (Fig. 1).

IMPORTANT ROLE OF ALDOSTERONE

In the early stages of cardiac failure, the heart is able to respond to the compensatory mechanisms. However, these mechanisms eventually lead to an increase in preload and afterload, further compromising cardiac function. The renin-angiotensin-aldosterone system becomes further activated by continued low cardiac output and decreased renal blood flow.[2]

The deleterious potential of these changes and concomitant therapy is suggested in Figure 2. The stimulation of the renin-angiotensin-aldosterone system with increased circulating aldosterone causes the distal renal tubules to secrete potassium, resulting in increased urinary potassium loss. The vigorous use of diuretics, especially the more potent loop diuretics, further stimulates the release of aldosterone, and can be additive leading to hypokalemia, thus increasing the risk of ventricular arrhythmias.

Not only does aldosterone play a key role in terms of potassium metabolism, but it also relates to magnesium metabolism. In clinical studies the administration of intravenous aldosterone resulted in increased urinary excretion of magnesium ions.[3] In this context, hypokalemia and hypomagnesemia, or some combination thereof, predispose the patient to increased ventricular ectopic activity.[4]

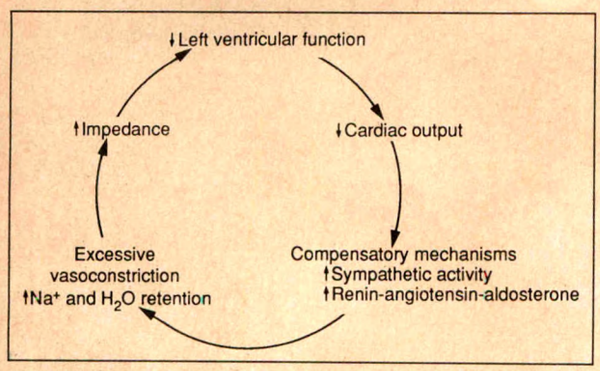


FIGURE 1. Compensatory mechanisms in congestive heart failure. H_2O = water; $\uparrow Na^+$ = increased sodium. (Adapted from *Medical Education Programs, Ltd.*[2])

Such a sequence of mechanisms in patients with CHF can substantially add to the other already significant existing factors predisposing to sudden cardiac death, which is the terminal event in up to 50% of patients with CHF.[1] These significant ramifications have had an increasing impact on therapeutic decision-making, and on the increased recognition of the practicing physician to the importance of monitoring and managing serum electrolytes, since this is one of the few correctable factors in these patients.

Figure 3 further illustrates the complex interactions of the multiple factors exacerbating ventricular arrhythmias in patients with CHF.

Therapeutic agents, from diuretics to inotropic drugs, such as digitalis and antiarrhythmic drugs—which can frequently be proarrhythmic in this context—can interact with neurohormonal changes to cause life-threatening arrhythmias.

Angiotensin II may also exacerbate electrolyte-related ventricular ectopy by promoting aldosterone-mediated losses of potassium and magnesium by the kidney, or angiotensin II may be directly proarrhythmic in its ability to potentiate the central and peripheral actions of the sympathetic nervous system. Consequently, both neurohormonal systems not only aggravate ventricular loading conditions by causing systemic vasoconstriction, but also may induce ventricular tachyarrhythmias by their direct and indirect actions on myocardial conduction and excitability.[5]

ELECTROLYTE CHANGES AND ARRHYTHMOGENIC POTENTIAL

The importance of electrolyte changes and their arrhythmic potential has been increasingly recognized. In hypertensive patients, Holland et al[6] reported that 7 of 21 patients with mild hypertension, being treated with a thiazide diuretic, exhibited an increase in both the frequency and the complexity of ventricular ectopic activity on Holter monitoring. The ventricular ectopic activity normalized with potassium repletion therapy. Hollifield and Slayton[7,8] performed a series of studies relating outpatient thiazide therapy for hypertension to arrhythmias. Ventricular premature contractions (VPCs) with static

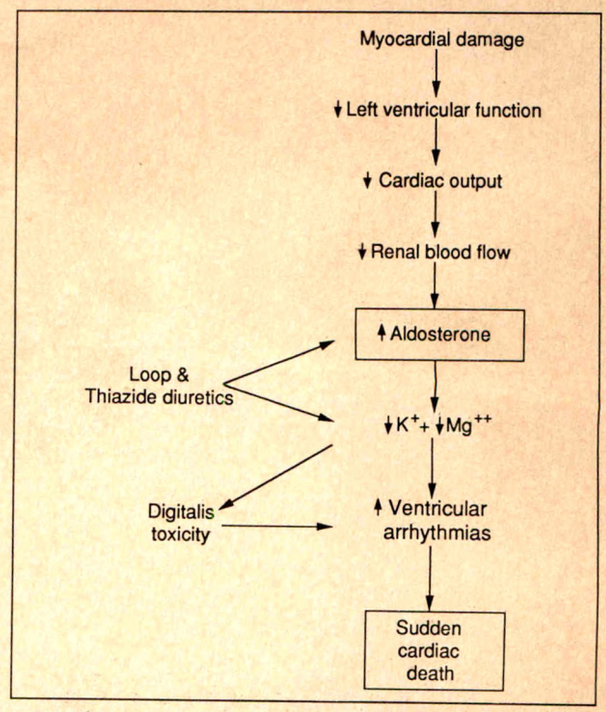


FIGURE 2. Causes and potential deleterious effects of potassium (K^+) and magnesium (Mg^{++}) depletion in congestive heart failure.

or dynamic exercise were unchanged during the pretreatment phase. However, with hydrochlorothiazide treatment, VPCs increased with both static and dynamic exercise. There also was a clear relation between the frequency of VPCs and the serum potassium level.

Of additional potential importance to the treatment of CHF, Hollifield and Slayton[4] also found a correlation between the frequency of VPCs and changes in the magnesium level (Fig. 4). In this study, a significant decrease in the frequency of VPCs did not take place with potassium or magnesium treatment alone, but did decrease to control values with combination potassium/magnesium

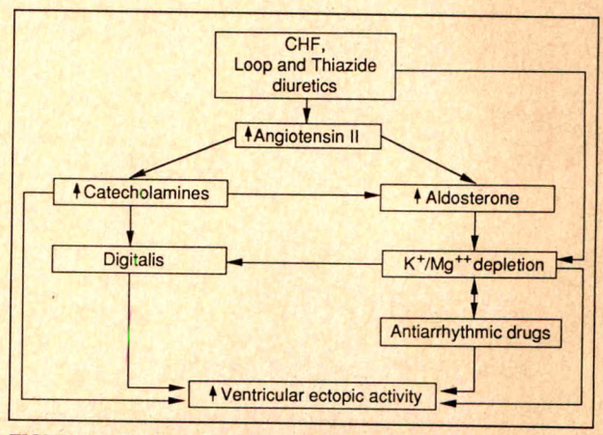


FIGURE 3. Exacerbation of ventricular arrhythmias. CHF = congestive heart failure; K^+ = potassium; Mg^{++} = magnesium. (Adapted from *Am J Med.*[5])

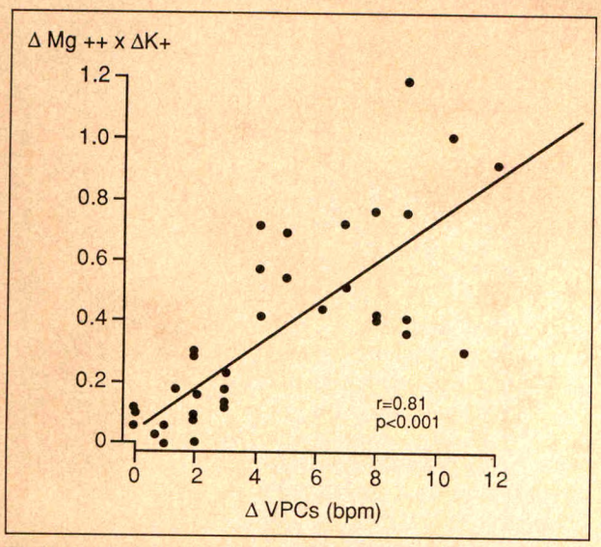


FIGURE 4. Electrolyte changes are linked with ventricular premature contractions (VPCs). The greater the change in the internal cationic milieu of the body, the greater the probability that the physician will see abnormalities in cardiac rhythm. This chart correlates the product of the change in serum magnesium (Mg) and serum potassium (K^+) with the occurrence of the ventricular premature contractions. The results show that a decrease of both potassium and magnesium correlates best with diuretic-associated ventricular ectopy. (Adapted from *London: Royal Society of Medicine.*[4])

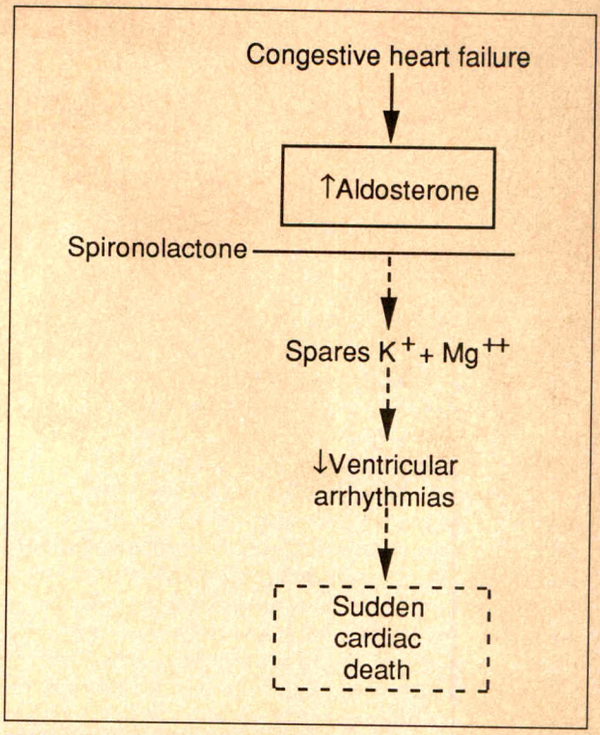


FIGURE 5. Beneficial mechanisms of spironolactone in patients with congestive heart failure. Spironolactone competitively antagonizes the action of aldosterone. The resultant potassium (K^+)-sparing and magnesium (Mg^{++})-sparing action is a logical means of reducing the potential of ventricular arrhythmias and ameliorating the risk of sudden cardiac death in patients with congestive heart failure.

therapy. These observations suggest that both potassium and magnesium are important electrolytes in relation to ventricular arrhythmias.

The relation of serum potassium and ventricular arrhythmias has also been shown in patients with acute myocardial infarction. Studies have demonstrated that the frequency of ventricular fibrillation was substantially greater in patients with acute myocardial infarction who were hypokalemic than in those who were normokalemic.[9]

Antiarrhythmic agents, although frequently administered to patients with CHF who have ventricular arrhythmias, have been shown to be less valuable in the presence of heart failure, with certain antiarrhythmic agents having a greater potential to induce arrhythmias.[10]

Spironolactone can favorably modulate the action of aldosterone, resulting in potassium- and magnesium-sparing (Fig. 5). Because of the fact that optimizing potassium and magnesium serum levels is one of the important and controllable variables in this syndrome, they should be monitored carefully in patients with CHF.

CONCLUSIONS

Potassium and magnesium depletion clearly can exert direct arrhythmogenic effects. Potassium depletion clearly can potentiate arrhythmias due to digitalis or catecholamine excess, or both. Certainly, catecholamine excess is inherent in advanced heart failure and digitalis continues to be an important therapy in advanced heart failure as well. In addition, potassium depletion can decrease the efficacy of antiarrhythmic drug therapy and may actually enhance the proarrhythmic potential of antiarrhythmic agents.

Because the treatment of arrhythmias in patients with CHF is a serious clinical problem, every effort should be made to reduce the predisposing factors leading to increased arrhythmogenesis, particularly decreased potassium and magnesium levels.

REFERENCES

1. Packer M. Sudden unexpected death in patients with congestive heart failure: A second frontier. *Circulation 1985;72:681–685.*

2. Dyckner T. Potassium/magnesium depletion in patients with cardiovascular disease. Scientific proceedings, Congestive heart failure and considerations of magnesium and potassium depletion as risk factors. Nov. 20, 1987. *Wilton, CT: Medical Education Programs, Ltd: 60–86.*

3. Horton R, Biglieri EG. Effect of aldosterone on the metabolism of magnesium. *J Clin Endocrinol Metab 1962;22:1187–1192.*

4. Hollifield JW, Slaton PE. Cardiac arrhythmias associated with diuretic induced hypokalaemia and hypomagnesaemia. In: Wood C, Somerville W, eds. Arrhythmias and Myocardial Infarction: The Role of Potassium. *London: Royal Society of Medicine, 1981;17–24.*

5. Packer M, Gottlieb SS, Kessler PD. Hormone-electrolyte interactions in the pathogenesis of lethal cardiac arrhythmias in patients with congestive heart failure: basis of a new physiologic approach to control of arrhythmia. *Am J Med 1986;80:suppl 4A:23–29.*

6. Holland OB, Nixon JV, Kuhnert L. Diuretic-induced ventricular ectopic activity. *Am J Med 1981;78:762–768.*

7. Hollifield JW, Slaton PE. Thiazide diuretics, hypokalemia and cardiac arrhythmias. *Acta Med Scand [Suppl] 1981;647:67–73.*

8. Hollifield JW. Potassium and magnesium abnormalities: diuretics and arrhythmias in hypertension. *Am J Med 1984;77:28–32.*

9. Helfant RH. Hypokalemia and arrhythmias. *Am J Med 1986;80:suppl 4A:13–22.*

10. Swan HJC. Introduction to a symposium. Meeting of the minds: treatment of arrhythmias in congestive heart failure. *Am Heart J 1987;114:1266.*

Relation of Cardiovascular Disease to Potassium and Magnesium Deficiencies

Thomas Dyckner, MD

Potassium and magnesium deficiencies, particularly those induced by conventional loop and thiazide diuretic therapy, have been linked in clinical studies to an increased frequency in serious arrhythmias and mortality in acute myocardial infarction. Magnesium repletion has been shown not only to increase magnesium levels, but also to increase muscle potassium and to decrease the frequency of ventricular ectopic beats. Potassium replenishment alone may have a detrimental effect in magnesium-depleted patients. The potassium-sparing diuretic spironolactone (Aldactone®) has been shown to spare both potassium and magnesium, and may therefore be a more appropriate diuretic therapy in patients at cardiovascular risk.

(Am J Cardiol 1990;65:44K–46K)

From Nacka Hospital, Nacka, Sweden.

Address for reprints: Thomas Dyckner, MD, Department of Internal Medicine, Nacka Hospital, S-13183 Nacka, Sweden.

The clinical importance of both potassium and magnesium levels has been observed in patients receiving digitalis or diuretics. These observations point to clinical implications connecting hypokalemia and hypomagnesemia with cardiac arrhythmias.

INCREASED RISK OF DIGITALIS-INDUCED ARRHYTHMIAS IN PATIENTS WITH CONGESTIVE HEART FAILURE RECEIVING DIURETICS

The combination of congestive heart failure (CHF) and diuretic therapy may lead to magnesium and potassium depletion (Fig. 1). If a patient is magnesium-depleted, any attempt to replete potassium may be inhibited by magnesium depletion. The combination of potassium and magnesium depletion has been shown to increase the risk for digitalis-induced arrhythmias. Sodium and calcium-dependent oscillatory afterpotentials, which contribute to digitalis-induced arrhythmias, may also be caused by magnesium depletion.[1]

POTASSIUM AND MAGNESIUM DISTURBANCES IN PATIENTS WITH CONGESTIVE HEART FAILURE RECEIVING DIURETICS

In a recent study[2] involving 297 patients with CHF who were treated with conventional diuretics, biopsy specimens of skeletal muscle were obtained, evaluated for potassium content and compared with those of normal control subjects. Plasma electrolytes were also obtained and compared with normal controls.

Decreased tissue potassium: A comparison of normal control subjects and diuretic-treated patients with CHF revealed significantly lower levels of skeletal muscle potassium in the diuretic-treated group (Fig. 2). Muscle potassium levels were below normal in 52% of the diuretic-treated patients.[1] In a review of 23 tissue potassium studies, decreases in muscle potassium were observed in all 23 studies, and in 11 of the 23 the decrease was statistically significant.[2]

Decreased tissue magnesium: Similar findings were seen with muscle magnesium depletion, with low levels of muscle magnesium occurring in 43% of the diuretic-treated patients with CHF (Fig. 2).[1]

Prevalent hypokalemia and hypomagnesemia: In the CHF/electrolyte study, hypokalemia was observed in approximately 42% of patients with CHF, and hypomagnesemia in approximately 37% (Fig. 2).[1] Among hypokalemic patients in general, hypomagnesemia has been shown to occur concurrently in 42% of cases.[2]

SERUM POTASSIUM IS NOT A PREDICTOR OF POTASSIUM/ MAGNESIUM DISTURBANCES

Although these data (Fig. 2) show a correlation between potassium and magnesium disturbances, a serum potassium determination is considered an unreliable method of predicting muscle potassium level, because of individual variations between muscle and serum potassium levels. When serum potassium and tissue potassium levels were compared in a recent analysis, no significant overall correlations were revealed.[2]

HYPOKALEMIA PREVALENT AMONG DIURETIC-TREATED PATIENTS WITH MYOCARDIAL INFARCTIONS

In patients with cardiovascular disease, diuretic therapy has been linked to deficiencies in potassium and magnesium. Hypokalemia (i.e., serum potassium <3.5 mmol/liter) has been shown to occur in approximately 50% of this population. Among thiazide-treated patients with acute myocardial infarctions, hypokalemia has been observed in approximately 15% of cases, and the in-hospital mortality has been shown to be increased among those who were hypokalemic compared with normokalemic patients. Furthermore, in patients with acute myocardial infarction, serious arrhythmias occurred more frequently among the hypokalemic than among normokalemic patients.[2]

MAGNESIUM: ESSENTIAL TO MAINTAINING POTASSIUM

Study results with potassium replenishment in patients who were magnesium-deficient and had CHF have shown that the body's magnesium status plays an important role in potassium metabolism, that potassium supplementation alone was ineffective in the maintenance of intracellular potassium,[2] and that potassium replenishment may have a detrimental effect in magnesium-depleted patients with CHF.[1]

These study results confirm earlier observations by Montgomery,[3] in which malnourished children were shown to have decreased muscle potassium and magnesium levels; by Shils,[4] in which total exchangeable potassium decreased during the period of deficiency and was not restored by potassium supplementation, but magnesium repletion was linked to an increase in total exchangeable potassium; and by Caddell and Olson,[5] in which potassium and magnesium depletion occurred concurrently in malnourished children.[6]

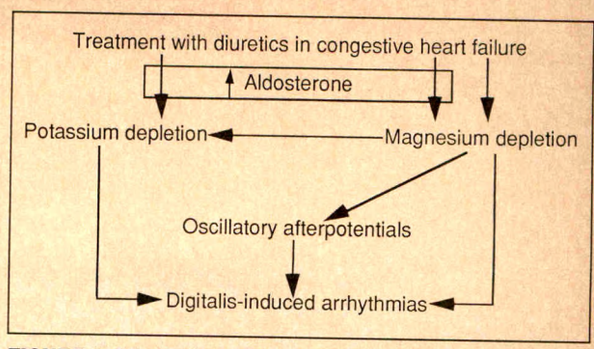


FIGURE 1. Mechanism of electrolytes and digitalis-induced arrhythmias. (Adapted from *Am J Med.*[2])

MAGNESIUM: EFFECT ON HEART ACTIVITY

Studies have also shown that magnesium ion influences the activity of the heart's function. Although its exact mechanism has not been established, it has been theorized that magnesium acts on sodium-potassium adenosine triphosphatase, and that a magnesium deficiency, through the action on sodium-potassium adenosine triphosphatase, leads to a cellular loss of potassium and an eventual decrease in intracellular potassium concentration with a concurrent normal serum potassium value.[6]*

BENEFICIAL EFFECT OF POTASSIUM AND MAGNESIUM IN ACHIEVING ADENOSINE TRIPHOSPHATASE ACTIVITY

It has been shown that magnesium and potassium are required to achieve adenosine triphosphatase activity. Although potassium activates this enzyme, the activation

*This mechanism has not been demonstrated in vivo. However, it has been shown in vivo that magnesium decreases the outflow of potassium from the cell.

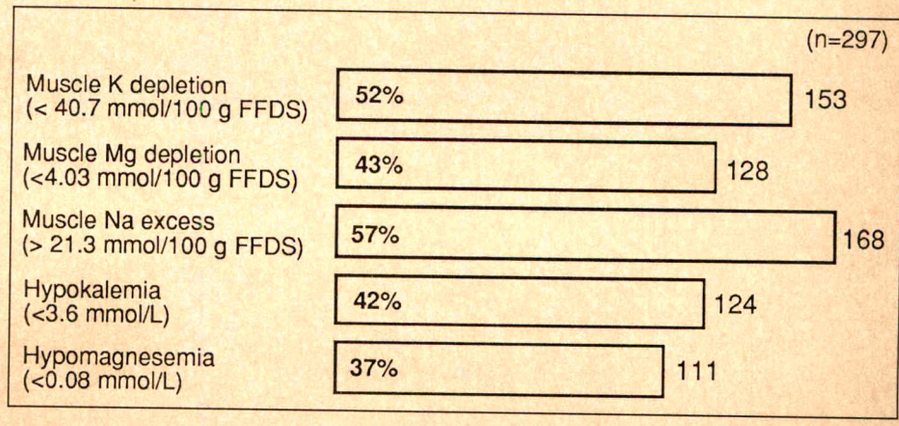


FIGURE 2. Incidence of electrolyte abnormalities among diuretic-treated patients with congestive heart failure. FFDS = fat-free dry solids; K = potassium; Mg = magnesium; Na = sodium. (Adapted from *Am J Med.*[2]).

TABLE I Potassium Replenishment: Detrimental Effect in Magnesium-Depleted Congestive Heart Failure

Pt Population	Before	After	p
Mg^{++}/m (n = 79)	K/pl 3.55 ± 0.61	4.30 ± 0.50	
67 Mg depleted	K/m 40.5 ± 4.74	39.2 ± 5.73	NS
+ 12 normal			
Normal	K/pl 3.33 ± 0.61	4.18 ± 0.66	
Mg^{++}/m (n = 12)	K/m 39.1 ± 2.83	43.0 ± 3.78	<0.02

FFDS = fat-free dry solids; K = potassium; m = muscle (mmol/100 g FFDS); Mg = magnesium; NS = not significant; pl = plasma (mmol/liter).
Adapted from *Am J Med.*[2]

occurs only in the presence of magnesium. Thus, replenishment with potassium alone has been shown to induce an increase in serum potassium, but not in muscle potassium.[2,6]

INFUSION STUDY CONFIRMS BENEFICIAL EFFECT OF MAGNESIUM

When a group of patients received separate infusions of potassium and magnesium, the magnesium-infused group had significant increases in not only magnesium but also potassium. In addition, these increases occurred in both serum and muscle. But in the group receiving the potassium infusions, 2 different effects were observed: first, a significant increase in serum potassium, and second, a statistically significant decrease in muscle magnesium and in muscle potassium.[2,6]

FAVORABLE EFFECT OF MAGNESIUM ON VENTRICULAR ECTOPY

We also investigated the frequency of ventricular ectopic beats in these same 2 groups of diuretic-treated, potassium- or magnesium-infused patients. Our study showed a significant increase in cellular potassium and a significant decrease in the frequency of ventricular ectopic beats among the magnesium-infused patient group only. In the potassium-infused group, no increase in cellular potassium or change of frequency of ventricular ectopic beats was observed.[2,6]

POTASSIUM DEFICIENCY: INCREASED RISK OF SUDDEN DEATH

Several studies involving diuretic-treated patients with CHF have shown an increased frequency of ventricular ectopic beats and this patient group has been shown to be at increased risk of sudden cardiac death. It has been speculated that the arrhythmias in these patients may be the result of a disturbance of the intracellular/extracellular potassium ratio secondary to magnesium deficiency caused by conventional diuretic therapy.[6]

DETRIMENTAL EFFECT OF POTASSIUM REPLENISHMENT

We conducted a study of 79 diuretic-treated, hypertensive patients with CHF who were hypokalemic and most of whom had a cellular magnesium depletion. We obtained muscle biopsy specimens before and after potassium replenishment (Table I).

Increased plasma potassium: The plasma potassium level increased from 3.55 to 4.30 mmol/liter.

Unchanged muscle potassium: The muscle potassium level showed no significant change. Twelve of the 79 patients had a normal muscle magnesium level, and in those 12 patients the potassium repletion resulted in a normalization of both serum and muscle potassium.

RESULTS

Incomplete potassium repletion: Our study results exemplified what typically occurs with potassium replenishment in patients with concomitant magnesium depletion, i.e., incomplete potassium repletion.

Incomplete potassium repletion is believed to occur because of the increase in serum potassium, since it has been shown that a serum potassium increase as small as 0.2 or 0.3 mmol/liter may induce an increase of aldosterone secretion by 50 to 100%, which in turn leads to an increased urinary loss of potassium and magnesium.[1]

CONCLUSIONS

Deficiencies in potassium and magnesium in conjunction with diuretic and digitalis therapy are associated with increased arrhythmias and increased mortality in patients with acute myocardial infarction. Magnesium replenishment is the key to potassium repletion. Maintenance of magnesium status is therefore essential in maintaining potassium status. Thus, a potassium/magnesium-sparing diuretic, such as spironolactone, is an appropriate therapy in patients with CHF at risk for potassium and magnesium deficiencies.

REFERENCES

1. Dyckner T. Potassium/magnesium depletion in patients with cardiovascular disease. Scientific proceedings, congestive heart failure and considerations of magnesium and potassium depletion as risk factors, Nov 20, 1987. *Wilton, CT: Medical Education Programs, Ltd: 60–86.*

2. Dyckner T, Wester PO. Potassium/magnesium depletion in patients with cardiovascular disease. *Am J Med 1987;82:suppl 3A:11–17.*

3. Montgomery RD. Magnesium metabolism in infantile protein malnutrition. *Lancet 1960;2:74–76.*

4. Shils ME. Experimental human magnesium depletion. *Medicine 1969;48:61–85.*

5. Caddell JL, Olson RE. An evaluation of the electrolyte status of malnourished Thai children. *J Pediatr 1973;83:124.*

6. Dyckner T, Wester PO. Ventricular extrasystoles and intracellular electrolytes before and after potassium and magnesium infusions in patients on diuretic treatment. *Am Heart J 1979;97:12–18.*

Role of Magnesium in Cardiac Tachyarrhythmias

Lloyd T. Iseri, MD

The efficacy of magnesium therapy in patients with ventricular tachycardia has previously been reported. Recently completed and ongoing studies validate earlier observations that potassium and magnesium supplementation may control other cardiac arrhythmias, particularly in hypomagnesemic patients. Magnesium treatment is a viable therapeutic option when other antiarrhythmic agents fail to suppress ventricular tachycardia, ventricular fibrillation, multifocal atrial tachycardia, atrial fibrillation and supraventricular tachycardia.

(Am J Cardiol 1990;65:47K–50K)

From the University of California, Irvine, California.

Address for reprints: Lloyd T. Iseri, MD, Cardiology Division, UCI Medical Center, 101 City Drive South, Orange, California 92668.

Magnesium deficiency is associated with a number of physiologic states such as inadequate dietary magnesium intake, use of loop and thiazide diuretics, digitalis toxicity, acute myocardial infarction, alcoholism, gastrointestinal losses, diabetes and congestive heart failure.[1–4] Clinical manifestations include several untoward cardiac effects (Table I).[5] Furthermore, although the mechanisms remain unclear, a causal relation between decreased serum magnesium and cardiac arrhythmias has been documented.[6,7] This association has prompted investigators to examine the possible effects of magnesium supplementation in patients with arrhythmias such as ventricular tachycardia (VT), ventricular fibrillation (VF), multifocal atrial tachycardia (MAT) and supraventricular tachycardia. Documented clinical data provide evidence that magnesium supplementation controls cardiac arrhythmias unresponsive to other therapy.

MAGNESIUM AND VENTRICULAR TACHYCARDIA

Both digoxin-induced tachyarrhythmias and those re sistant to digoxin therapy have been treated successfully with magnesium supplementation. We reported our initial experience with magnesium infusion in patients with VT and VF in 1975.[8]

Recently, magnesium sulfate ($MgSO_4$) (2 g infused over 1 minute, followed by a 10-g infusion over 5 hours) controlled arrhythmic dysfunction in 12 patients with intractable VT and VF with clear documentation in 10 cases.

VF and VT were present in 5 patients, VT alone in 4 patients and VF alone in 1. In the patients with VT, torsades de pointes was observed consistently in 2 and intermittently in 3. Laboratory values revealed low serum magnesium levels in only 3 patients. Cardiac arrhythmias were refractory to treatment with lidocaine, bretylium, procainamide hydrochloride, phenytoin sodium, amiodarone and mexiletine. Countershock treatment or overdrive pacing failed to control the tachyarrhythmia in 8 of these patients.

Serum magnesium levels increased in direct relation to the rate of magnesium infusion. During the study, administration of magnesium, 20 mEq/hour for approximately 5 hours increased serum values to supernormal (4 mEq/liter) levels. Eleven of 12 patients converted to sinus or paced rhythm within 5 minutes of the 2-g infusion of magnesium. The following 3 cases of particular interest are highlighted.

Case 1: A female patient with marked congestive heart failure due to coronary artery disease developed intractable VT after 10 days of intensive therapy. Elec

CAL. CENTRAL LIBRARY

TABLE I Hypomagnesemia-Induced Cardiac Effects

Ventricular premature contractions and ventricular tachyarrhythmia
Prolonged PR and QT intervals
T-wave flattening
Atrial fibrillation and supraventricular tachycardia
Torsades de pointes
Coronary artery spasm
Increased sensitivity to digitalis
More extensive myocardial infarction
Possibly increased sensitivity to ventricular fibrillation and sudden death in ischemic heart disease

trocardiography showed a change in direction of VT, characteristic of torsades de pointes; however, the QT interval was not prolonged. Serum potassium was 4.7 mEq/liter; serum magnesium, 1.9 mEq/liter; serum digoxin, 1.4 ng/ml; and quinidine, 3.3 μg/ml.

Initial treatment with lidocaine and bretylium failed to control the VT. Administration of magnesium as a 2-g bolus over 1 minute and 10 g over 5 hours succeeded in suppressing the VT. Continuous electrocardiographic (ECG) monitoring during drug infusion demonstrated a rapid and dramatic decrease in the number of ectopic beats.

Case 2: A 50-year-old man who was admitted with mitral valve prolapse after ingestion of 100 digoxin tablets in a suicide attempt was experiencing periods of sinus arrest and atrioventricular block 4 hours later. ECG findings were sporadic occurrence of P waves with junctional escape beats. Complete heart block alternating with VF ensued. Serum digoxin was 20 ng/ml; potassium, 4.0 mEq/liter; magnesium, 2.7 mEq/liter; and calcium, 8.6 mg/dl. Despite intravenous administration of lidocaine and phenytoin, the patient had 18 episodes of VF which required countershock treatment.

A dose of 12 g of magnesium raised serum magnesium to 3.9 mEq/liter and controlled VF. A transvenous pacer controlled the heart block. In this patient, magnesium infusion corrected the increase in serum potassium known to occur subsequent to massive digoxin poisoning.[9] Initially, serum potassium increased from 4.0 to 4.8 mEq/liter, and finally to 5.7 mEq/liter. After administration of magnesium, the potassium level decreased to 4.8 mEq/liter.

Case 3: A male patient with advanced coronary artery disease had cardiac arrest 3 days before admission to the hospital. ECG monitoring demonstrated a series of polymorphic VT tracings resembling torsades de pointes, with a rate as frequent as 260 beats/min. Between episodes, the QTc was 492 ms. VT was resistant to overdrive pacing and administration of lidocaine, amiodarone, verapamil, atenolol and mexiletine. Baseline laboratory studies showed a normal serum magnesium level of 1.6 mEq/liter. The VT episode disappeared after intravenous administration of magnesium.

Monomorphic VT recurred at 48 and 84 hours, associated with a decrease in serum magnesium (1.2 to 1.3 mEq/liter). Each episode was controlled with additional $MgSO_4$. Although the patient received 37 g of $MgSO_4$ over 7 days, he remained hypomagnesemic, suggesting renal tubular injury that probably occurred during the initial cardiac arrest. The fractional excretion for magnesium was 11% and retention of administered magnesium was only 28%. Considering his hypomagnesemic state, these values should have been <3% and >50%, respectively.

Oral magnesium chloride, 2 tablets 3 times daily, and amiodarone controlled VT for 1 year, after which the patient had a fatal series of recurrent VT.

MAGNESIUM AND MULTIFOCAL ATRIAL TACHYCARDIA

Although MAT is usually associated with pulmonary insufficiency, it may also occur in cardiac failure. The rhythm is characterized by at least 3 different foci of pacemaker function in the atria, 1 of which may be the sinus node. The ventricular response is irregular, sometimes mimicking atrial fibrillation. It is often misdiagnosed, and excessive administration of digitalis may result in toxicity, with resultant VT and VF. A prospective study[10] evaluated efficacy of parenteral magnesium therapy in controlling MAT.

Eight patients, 3 men and 5 women (aged 52 to 76 years, mean 69) were enrolled in the study. Five patients had chronic obstructive pulmonary disease, 2 had congestive heart failure, and 1 had chronic brain syndrome with recurrent pneumonia. Diagnostic criteria for MAT included heart rate >100 beats/min, at least 2 separate ectopic pacemaker sites with abnormal P-wave contour in addition to the sinus node identifiable in the electrocardiogram, and variability of RR, PP and PR intervals.

Susceptibility to MAT may be enhanced by chronic depletion of magnesium and potassium, which can be caused by chronic respiratory failure with hypoxia, recurrent use of diuretics, and use of gentamicin, among other factors. Six of the study enrollees received theophylline throughout the study, and 1 patient was given an infusion of dopamine at a constant rate over the course of the study. Five patients received furosemide 24 hours before study initiation; 2 received gentamicin. During the study, 6 patients received digoxin therapy; however, none had elevated serum digoxin levels. No patient was oliguric or had renal failure.

Persistent MAT was established in all patients after a 2-hour observation period. Each patient was monitored constantly with electrocardiography and frequent arterial blood gas studies. Baseline electrocardiogram and serum potassium and magnesium levels were recorded. Intravenous magnesium (20% solution), 10 ml, was infused over 1 minute, followed by 250 to 500 ml (2% solution) over the next 5 hours. One patient received 500 ml over a 10-hour period. Supplemental potassium was given to 3 patients with low serum levels (<4 mEq/liter), and 3 other patients received potassium later when their serum levels decreased below 3.5 mEq/liter. At 2, 4, 8 and 16 hours after drug administration, a 20- to 30-second ECG rhythm strip was obtained. Ectopic atrial activity (abnormal P-wave contour) and ventricular rate (QRS complexes) were counted.

During magnesium infusion, serum levels increased from an average of 1.64 mEq/liter to a maximal average of 3.49 mEq/liter. After discontinuance of the infusion,

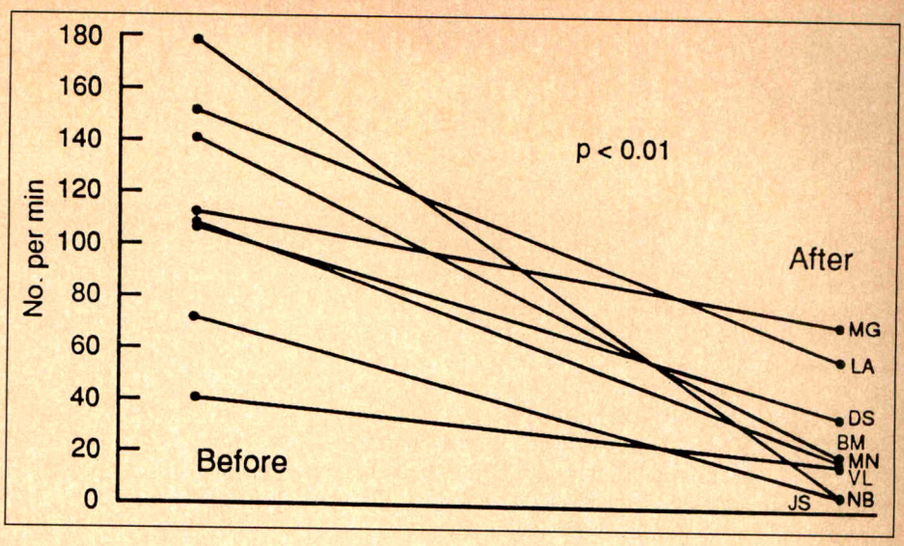


FIGURE 1. Ectopic atrial activity. Changes in frequency of ectopic atrial activity after magnesium and potassium infusion. Initials are those of individual patients. (Adapted from *Am Heart J.*[10])

the levels began to decrease, approaching normal within 10 to 16 hours. Serum potassium levels, in the absence of supplementation, decreased significantly. This reduction was reversed with concomitant administration of potassium.

In 7 of the 8 patients, conversion of MAT to sinus rhythm or sinus tachycardia occurred after infusion (Fig. 1 and 2). In the remaining patient, ectopic atrial activity continued; however, ventricular rate was reduced to 87 beats/min, indicating conversion from MAT to multifocal atrial rhythm. In all patients, atrial ectopy increased in frequency and the ventricular rate accelerated 6 to 12 hours after administration of magnesium, suggesting that improvement in rhythm was not a coincidental event.

The depletion of tissue magnesium could lead to decreased cellular potassium; sodium and calcium are able to enter the cellular space, creating an ionic imbalance.[11] Although magnesium's mechanism of action is not clearly understood in controlling MAT, it is postulated that it acts as a natural calcium channel blocker.[12] Infusion of magnesium may prevent spontaneous depolarization by blocking the entry of calcium, as well as preventing release of free calcium within the atrial cell.[5]

The role of magnesium in supraventricular tachyarrhythmia is imprecise. Supraventricular arrhythmia, not MAT, in 5 patients treated with magnesium, converted to sinus rhythm. Hypomagnesemia was present in 4 of the 5 patients. Some unsuccessful results have been reported, which might indicate that a hypomagnesemic state requires a greater amount of magnesium to control tachyarrhythmia or that other factors are operating.

MAGNESIUM AND ATRIAL FIBRILLATION

Digoxin treatment of atrial fibrillation appears to be impaired in the presence of magnesium deficiency.[13] Preliminary observations of an ongoing, double-blind study evaluating the effect of magnesium replacement on ventricular rate and atrial fibrillation indicate efficacy of magnesium supplementation in reducing ventricular rate and converting atrial fibrillation into normal sinus rhythm.

CONCLUSIONS

Results from these studies as well as others have more clearly defined the role of magnesium in cardiac arrhythmias. The following conclusion summarizes what is now

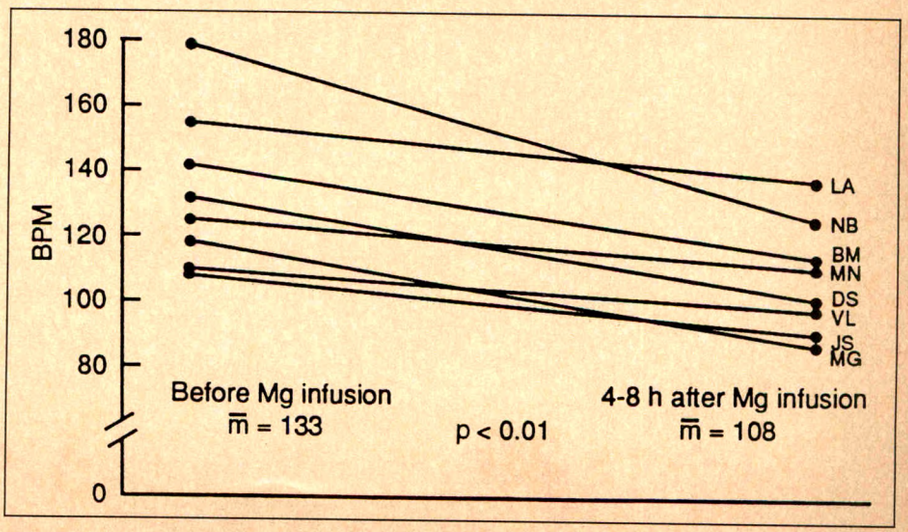


FIGURE 2. Ventricular rate. Effect of magnesium and potassium infusion on ventricular rate in multifocal atrial tachycardia. m = mean; mg = magnesium. Initials are those of individual patients. (Adapted from *Am Heart J.*[10])

known about the influence of magnesium on arrhythmias.

First, patients with cardiopulmonary disease, whether overtly symptomatic or asymptomatic, are highly susceptible to magnesium deficiency. Second, magnesium deficiency may be due to intrinsic cardiac/pulmonary disease and pulmonary insufficiency, may be iatrogenic (drug induced), or may be aggravated by physiologic disorders such as diabetes or alcoholism. Third, magnesium deficiency may not be revealed by low serum levels and may manifest itself with tachyarrhythmia without warning. Fourth, magnesium infusion in the absence of renal insufficiency is safe and may be very effective in controlling intractable VT and VF whether the patient is hypomagnesemic or normomagnesemic, or VT is monomorphic or polymorphic. Magnesium may be specific in torsades de pointes,[14] and it appears to be so for massive digoxin-intoxicated VT.[9] Magnesium supplementation is highly effective for MAT or for supraventricular tachycardia, when it is associated with hypomagnesemia.[10]

The recommended dosage is 20% magnesium, 10 to 15 ml infused over 1 minute, followed by 500 ml of 2% solution over 5 hours. Potassium chloride, 20 to 40 mEq, should be added if serum potassium is ≤4 mEq/liter. In addition, 500 ml of 2% magnesium may be given over 10 hours in patients who are severely hypomagnesemic. Deep tendon reflexes, blood pressure, magnesium and potassium levels, and ECG tracing should be monitored during infusion.

In patients who require maintenance therapy, oral magnesium chloride can be given. Enteric-coated magnesium chloride up to 32 mEq/day is well tolerated and may be effective in managing tachyarrhythmia.

REFERENCES

1. Whang R. Magnesium deficiency: pathogenesis, prevalence, and clinical implication. *Am J Med 1987;82:suppl 3A:24–29.*

2. Wacker WEC, Parisi AF. Magnesium metabolism. *N Engl J Med 1968;278: 658–776.*

3. Agus ZS, Wasserstein A, Golfarb S. Disorders of calcium and magnesium homeostasis. *Am J Med 1982;72:473–488.*

4. Elin RJ, Hosseini JM. Magnesium content of molecular blood cells. *Clin Chem 1985;31:377–380.*

5. Reinhart RA. Magnesium metabolism. A review with special reference to the relationship between intracellular content and serum levels. *Arch Intern Med 1988;148:2415–2420.*

6. Dyckner T. Serum magnesium in acute myocardial infarction. *Acta Med Scand 1980;207:59–66.*

7. Roden DM, Iansmith DHS. Effects of low potassium or magnesium concentrations on isolated cardiac tissue. *Am J Med 1987;82:suppl 3A:18–23.*

8. Iseri LT, Freed J, Bures AR. Magnesium deficiency and cardiac disorders. *Am J Med 1975;58:837–846.*

9. French JH, Thomas RG, Siskind AP, Brodsky M, Iseri LT. Magnesium therapy in massive digoxin intoxication. *Ann Emerg Med 1984;13:562–566.*

10. Iseri LT, Fairshter RD, Hardemann JL, Brodsky MA. Magnesium and potassium therapy in multifocal atrial tachycardia. *Am Heart J 1985;110:789–794.*

11. Kass RS, Lederer WJ, Tsien RW, Weingart R. Role of calcium ions in transient inward currents and after-contractions induced by strophanthidin in cardiac Purkinje fibers. *J Physiol (Lond) 1978;281:187–194.*

12. Iseri LT, French JH: Magnesium: nature's physiologic calcium blocker. *Am Heart J 1984;108:188–193.*

13. De Carli C, Sprouse G, LaRosa J. Serum magnesium levels in symptomatic atrial fibrillation and their relation to rhythm control by intravenous digoxin. *Am J Cardiol 1986;57:956–959.*

14. Tzivoni D, Keren A, Cohen AM, Loebel H, Zahavi I, Chenzbraun A, Stern S. Magnesium therapy for torsades de pointes. *Am J Cardiol 1984;53:528–530.*

Spironolactone in the Management of Congestive Heart Failure

James E. Muller, MD

Although many new drugs useful in the treatment of congestive heart failure have been introduced during the past 25 years, spironolactone continues to have an important role in the management of this condition. Spironolactone adds to the activity of the thiazide and loop diuretics to enhance the elimination of sodium and water. Furthermore, unwanted electrolyte disturbances such as hypokalemia and hypomagnesemia, associated with the administration of other classes of diuretics, can be minimized with spironolactone.

(Am J Cardiol 1990;65:51K–53K)

Treatment of patients with congestive heart failure (CHF) has traditionally involved the use of diuretics, digitalis and (in recent years) a vasodilator. Diuretics promote the excretion of sodium and water, thereby relieving the circulatory congestion associated with CHF; digitalis is used to increase the inotropic state of the heart; and a vasodilator is usually added to the treatment regimen of patients with CHF to reduce the afterload of the heart.

Although thiazide diuretics (such as hydrochlorothiazide) and loop diuretics (such as furosemide) are initially effective, diuretic effects may be reduced after continued use. Furthermore, they may be associated with electrolyte depletion (mainly potassium and magnesium), which can lead to hypokalemia and the potential for the generation of arrhythmias with or without the presence of the cardiac glycosides. As more becomes known about these long-term, potentially arrhythmogenic effects, a potassium-sparing diuretic is frequently used in patients with CHF along with a thiazide or loop diuretic. Spironolactone (Aldactone®) is the best known potassium-sparing diuretic, and has acquired the longest record of proved clinical effectiveness and safety over 25 years.

MECHANISMS OF DIURETIC ACTION

Potassium-sparing diuretics act in the distal and late distal convoluted tubules, and the cortical collecting tubules, which are major sites of potassium secretion. The distal convoluted tubule is also the site of action of aldosterone (Fig. 1).

In contrast, thiazide diuretics and other agents with strong diuretic action block the reabsorption of sodium in the ascending section of the loop of Henle and the cortical segments of that portion of the nephron. Without potassium-sparing diuretic therapy, this action causes an excess sodium load to be delivered to the distal tubules and cortical collecting tubules. The result: increased sodium absorption in exchange for secreted potassium in these distal segments of the nephron and consequent increase in potassium secretion (Fig. 1).

Because of the differing anatomic sites of action between potassium-sparing diuretics vs thiazide or loop diuretics, a potassium-sparing diuretic may have an additive effect if used in addition to a loop diuretic, or vice versa.

PHYSIOLOGIC BENEFITS OF THE ALDOSTERONE ANTAGONIST SPIRONOLACTONE

A potassium-sparing diuretic controls the reabsorption of sodium in the distal segments and thereby inhibits potassium secretion. The aldosterone antagonist spirono-

From the Harvard Medical School, Boston, Massachusetts.
Address for reprints: James E. Muller, MD, Harvard Medical School, 164 Longwood Avenue, Boston, Massachusetts 02115.

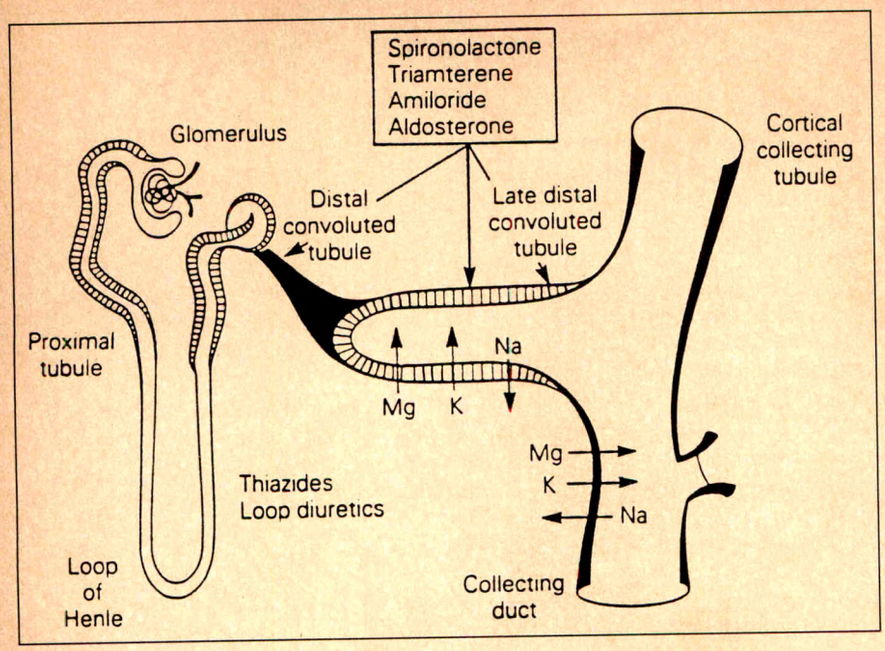


FIGURE 1. Mechanisms of diuretic action. K = potassium; Mg = magnesium; Na = sodium.

lactone (Aldactone) modulates the action of aldosterone at the sodium-potassium exchange site of the distal convoluted tubule.

In the presence of spironolactone therapy, aldosterone molecules are preempted from aldosterone receptor-binding sites. Through this potassium-sparing physiologic action, spironolactone has also been shown to block renal excretion of magnesium, and may therefore be useful in counteracting magnesium deficiency often seen in diuretic-treated patients.[1–5]

Triamterene and amiloride, the other 2 potassium-sparing diuretics, are less potent than spironolactone, and therefore must almost always be combined with thiazide therapy to be clinically effective. Exactly how triamterene works is not clearly understood. It presumably causes a decrease in the transtubular potential difference, which promotes sodium excretion and blocks potassium secretion. Unlike spironolactone, neither triamterene nor amiloride act by mineralocorticoid antagonism (i.e., aldosterone antagonism). Their overall effect is to block sodium hydrogen and sodium potassium exchange in the distal tubule.[5]

Of the 3 potassium-sparing diuretics, spironolactone closely mimics the chemical structure of aldosterone.

The close chemical similarity of the aldosterone and spironolactone molecules helps to explain many of their interrelated effects, among them the competitive antagonism of aldosterone by spironolactone.

At the molecular level, aldosterone is thought to bind to a specific mineralocorticoid receptor present in the cytosol of the target cells, thus creating a physiologic advantage by which spironolactone is believed to compete with aldosterone for binding to this receptor.[6] Other potassium-sparing agents lack this physiologic link to aldosterone.

Without spironolactone's physiologic advantage of modulating aldosterone binding, aldosterone-mediated enhancement of potassium excretion may further exacerbate diuretic-induced hypokalemia and hypomagnesemia.[6] Aldosterone not only causes urinary loss of magnesium, but also promotes urinary excretion of potassium.[6]

BENEFICIAL EFFECT ON ELECTROLYTES

Although much is known clinically about the dangers of diuretic-induced potassium depletion, there is an increase in published reports on the dangers of magnesium depletion as well.

Dyckner and Wester[7] concluded from their studies that normal doses of conventional diuretics result in a 25 to 50% increase in urinary loss of magnesium.

Because magnesium is needed for the transport of potassium into cells, potassium supplementation may be insufficient to replenish potassium stores in magnesium-deficient patients. Magnesium deficiency is thought to impair the activity of the key transport enzyme, adenosine triphosphatase, which governs the transport of potassium across cell membranes. Thus, the potassium- and magnesium-sparing diuretic spironolactone has several clinical benefits compared with other diuretics used in CHF.

Long-term treatment with thiazide and loop diuretics may lead to: reduction in effective plasma volume, reflex activation of the renin-angiotensin-aldosterone system, a consequent increase in aldosterone secretion, sodium and water retention resulting from increased aldosterone, enhancement of potassium excretion, exacerbation of diuretic-induced hypokalemia and hypomagnesemia, hyperuricemia, hyperglycemia, and adverse effects on serum lipids.

These effects may be minimized by the concomitant use of spironolactone, since it is an aldosterone antagonist. Spironolactone has been shown in clinical trials to minimize hypokalemia induced by diuretics in patients with CHF and hypertension. Spironolactone is also de-

void of many undesirable metabolic effects associated with thiazide and loop diuretics, including changes in uric acid, glucose, insulin and serum lipids.

Long-term spironolactone therapy has been shown to cause a minimal decrease in high-density lipoprotein concentrations, although these remain within the normal range. Thus, spironolactone may be appropriate not only in patients with mild to moderate CHF, but as concomitant medication in those with gout, lipid disorders or diabetes.[6]

DISCUSSION

The potassium- and magnesium-sparing diuretic spironolactone has some definite clinical benefits, including prevention of potentially dangerous hypokalemia without the use of potassium supplements, prevention of unrecognized magnesium deficiency, and the avoidance of the need for potassium supplements, which can be associated with several adverse effects, whether administered alone or concomitantly with a conventional diuretic or a potassium-sparing diuretic.

By using spironolactone without potassium supplements or other potassium-sparing agents and avoiding its use in cases of renal failure, it can be used with clinical safety.[2]

Angiotensin-converting enzyme (ACE) inhibitors are now widely used for the treatment of CHF. Because an ACE inhibitor by itself can raise potassium levels, a potassium-sparing diuretic or salt substitute should not be used with an ACE inhibitor because the combination increases the risk of life-threatening hyperkalemia. Because ACE inhibitors block aldosterone increases, it would be expected that spironolactone would be of minimal value in patients receiving these agents. For this reason, the combination of potassium supplements and ACE inhibitors should also be avoided. This includes salt substitutes, some of which have a high potassium content.

Spironolactone's use is of particular importance in patients with CHF receiving thiazide or loop diuretics. In these patients, potassium and magnesium deficiencies have been associated with cardiac arrhythmias, increased ventricular ectopic beats, and risk of sudden death. Thus, prompt treatment of potassium and magnesium deficiencies is called for, to replenish both of these electrolytes, and thereby decrease the potential for these occurrences. Because serum levels may not actually reflect the extent of magnesium and potassium depletion, there are advantages to preventing depletion of both potassium and magnesium with a potassium/magnesium-sparing diuretic, i.e., spironolactone.[7,8]

REFERENCES

1. Beck LH, Kaplan NM, Mroczek WJ. When potassium therapy is needed. *Patient Care 1982;16:63–94.*

2. Muller JE. A review: spironolactone in the management of congestive cardiac failure. Scientific proceedings, congestive heart failure and considerations of magnesium and potassium depletion as risk factors, Nov 20, 1987. *Wilton, CT: Medical Education Programs, Ltd: 135–169.*

3. Dreslinski GR, Frohlich ED, Messerli FH, Batson HM. Diuretics. *Practical Cardiology 1980;6:132–145.*

4. Johnston JM, Kem DC. Differential diagnosis of hypokalemia. *Practical Cardiology 1977;3:17–27.*

5. Shoback DM, Williams GH. Potassium-sparing diuretics: clinical pharmacology and therapeutic uses. *Drug Therapy 1982;12:113–121.*

6. Muller J. Spironolactone in the management of congestive cardiac failure: a review. *Clin Ther 1986;9:63–76.*

7. Dyckner T, Wester PO. Potassium/magnesium depletion in patients with cardiovascular disease. *Am J Med 1987;82:suppl 3A:11–17.*

8. Dyckner T. Potassium/magnesium depletion in patients with cardiovascular disease. Scientific proceedings, congestive heart failure and considerations of magnesium and potassium depletion as risk factors. Nov 20, 1987. *Wilton, CT: Medical Education Programs, Ltd: 60–86.*

"Silent" Heart Failure as Observed by a French Cardiologist

Alain Castaigne, MD

As the precursor of overt heart failure, with its grim prognosis, "silent" heart failure is a concept that bears examination. The pathophysiology of congestive heart failure and the mechanisms of the impact of hypertension on the development of left ventricular hypertrophy, and silent and overt heart failure are investigated. In addition, the reasons why diuretics, especially potassium-sparing diuretics such as spironolactone, remain the most effective treatment of mild congestive heart failure, and their role in preventing the evolution of silent to overt heart failure are explained.

(Am J Cardiol 1990;65:54K–57K)

"Silent" heart failure is not a commonly used medical term but it is a term used to connote a potentially hazardous medical condition. It is the precursor of overt heart failure. Overt heart failure, once established, tends to become progressive with a very grim prognosis.

CONCEPT OF "SILENT HEART FAILURE"

Silent heart failure is the most common form of heart failure representing the early form of congestive heart failure (CHF). It is characterized by left ventricular hypertrophy (LVH) and some hemodynamic deficits, but at this point in time, exercise tolerance is not decreased and the patient is asymptomatic.

It is appreciated now that hypertension, untreated or uncontrolled, in a progression that will be described later, will sooner or later lead to heart failure, and so can be viewed as one of the precursors of heart failure. In this sense, hypertension itself could be viewed as having the potential to cause silent heart failure. The concept of silent heart failure that I am advancing is at the same stage today that the now-accepted concept of silent myocardial ischemia was a few years ago. Just as the recognition of silent myocardial ischemia and its identification are now helping to reduce the rate of myocardial infarction and sudden death, we should work toward a recognition and treatment of silent heart failure to prevent its progression to overt CHF with its attendant poor prognosis, namely, a 62% probability of death within 5 years of its first appearance in men with or without coronary heart disease.[1]

By now, the clinical progression of CHF through its various stages is well known, as are the pathophysiologic processes of CHF. There are various therapeutic ways to intervene in these processes, and to slow down or halt the progression of CHF, but if possible, it would seem that intervention at the silent stage, i.e., preventing rather than treating, would have many benefits—clinical, economic and social. The rational use of diuretics is an older approach in treating patients with CHF, and diuretics, particularly potassium-sparing diuretics such as spironolactone, either alone or in combination, are not only the most effective treatment of early CHF, but also can best assist in limiting the deadly progression of silent heart failure to overt heart failure.

INTERRELATION OF HYPERTENSION AND CONGESTIVE HEART FAILURE

Because a large proportion of patients with CHF have a history of hypertension, and because hypertension is known to predispose to heart failure, there is a definite possibility of some early form of silent heart failure in

From the University of Paris, France.

Address for reprints: Alain Castaigne, MD, Cardiology Department, Hôpital Henri Mondor, 94010 Créteil, France.

hypertensive patients, especially when the hypertension has been present for some time. In the Framingham Study, 75% of those who developed CHF during a 16-year observation period had prior hypertension.[1]

Hypertension and the heart are inextricably interrelated. On the one hand, the heart's contractile force supplies the energy that creates the blood pressure. On the other hand, in patients with chronic hypertension, LVH develops as a compensatory mechanism to maintain the heart's pumping function against increased systemic arterial pressure. Later, however, the hypertrophy can no longer keep pace with the overload, and significant left ventricular (LV) dysfunction occurs. LV dysfunction ultimately leads to heart failure, CHF making its appearance when the heart is no longer able to propel the blood foward normally (decreased cardiac output) in appropriate response to tissue needs. This decreased cardiac output then results in congestion in the pulmonary or systemic circulation, or both.

The Framingham Study has demonstrated that the risk of LVH increases with increasing levels of blood pressure, in both men and women.[2] In fact, there is a restructuring of LV geometry that begins at so-called "normal" blood pressure levels, i.e., below 140 mm Hg systolic. Even in normotensives, LV mass increases with age. Arterial hypertension accelerates these changes, eventually leading to LVH, heart failure and CHF.

PATHOPHYSIOLOGIC PROCESSSES IN CONGESTIVE HEART FAILURE

In heart failure, blood flow and blood pressure to the organs are compromised. To maintain arterial pressure at a level as close as possible to normal and to preserve normal coronary and cerebral blood flow, the sympathetic nervous system is activated, leading to enhanced release of norepinephrine, which stimulates both α- and β-adrenergic receptors.

The stimulation of β receptors in the myocardium causes an increase in heart rate and myocardial contractility. However, this stimulation is limited by the fact that heart rate cannot be increased too much without affecting ventricular filling. The stimulation of myocardial β receptors results in a desensitization of these receptors, which then become less and less responsive to increased levels of circulating catecholamines. Thus, higher levels of circulating catecholamines result in less effective β stimulation.

The stimulation of the α receptors leads to arteriolar vasoconstriction, which is unevenly distributed, depending on the number and sensitivity of α receptors in a given organ. For instance, blood flow to the skin and muscles, which are amply provided with α receptors, is decreased. On the other hand, the myocardium, the brain and respiratory muscles are only slightly affected by this noradrenergic α stimulation. In the kidneys, the arterial blood flow is directed toward the nephrons with the best filtration capacity, but these nephrons are also those with the best sodium-retaining capacity.

The stimulation of venous α receptors leads to venous constriction that results in an increase in venous return and intrathoracic blood volume. The stimulation of β receptors in the juxtaglomerular apparatus participates in the activation of the renin-angiotensin-aldosterone system: renin secretion is activated both by catecholaminergic stimulation, and by the decrease in perfusion pressure (blood flow) sensed by the afferent arterioles.

Enhanced renin release leads to the increased formation of angiotensin II, a potent vasoconstrictor, which acts synergistically with the noradrenergic nervous system. In one way, angiotensin II reinforces the vasoconstriction in the arteriolar areas already vasoconstricted and, in the other, it centrally activates the sympathetic nervous system, thus increasing the concentration of circulating catecholamines. Angiotensin II stimulates increased aldosterone production and release, leading to an increased rate of reabsorption of sodium at the distal tubules, and to increased potassium/magnesium excretion, resulting in sodium retention, potassium depletion, hypokalemia and hypomagnesemia. Sodium retention increases circulating blood volume and contributes to intrathoracic congestion. Sodium retention, along with the increase in filling pressure, is the cause of the pulmonary or peripheral edema seen in heart failure.

As a result, although arterial pressure and blood flow to the myocardium and the brain are adequately maintained (in mild heart failure), this results in decreased blood flow (and thus, reduced perfusion of some organs); as mentioned previously, the numerous α receptors in the skin are stimulated by the norepinephrine secreted in response to the activation of the sympathetic nervous system brought about by the decreased perfusion of vital organs, and the blood flow in the muscles and skin is thus decreased in favor of maintaining flow to the brain and heart—thus, the cold skin and progressive worsening of exercise tolerance. Two vicious cycles ensue for maintaining adequate perfusion of the myocardium and the brain: (1) vasoconstriction (leading to water and sodium retention), and (2) increase in LV systolic and diastolic load.

Vasoconstriction and water/sodium retention—the first vicious cycle in heart failure: The vasoconstrictor systems are antinatriuretic. Their function is to combat acute or prolonged decreases in blood pressure with the aid of a short-term weapon, vasoconstriction, and a long-term weapon, water and sodium retention.

Vasoconstriction leads to a water/sodium retention. The intrarenal hemodynamics in heart failure are disturbed in such a manner that it is those nephrons best able to retain sodium that unfortunately are preferentially perfused.

Aldosterone completes this antinatriuretic phenomenon. This is why one of the clearest clinical signs of cardiac failure is a decrease in natriuresis in response to a sodium load.

Sodium retention in turn potentiates the vasoconstriction: The capacity of smooth-muscle cells to react to vasoconstricting stimuli is related to intracellular calcium concentration, which is itself partly dependent on intracellular sodium concentration via a membrane sodium-calcium exchange mechanism. Thus, sodium retention is accompanied by an increase in the reactivity of smooth muscle cells to vasoconstrictor stimuli.

This is the first vicious cycle: The vasoconstriction needed to preserve blood flow to the brain and myocardium leads to sodium retention by maintaining adequate blood flow in the sodium-retaining nephrons. This sodium retention increases the reactivity of the smooth muscle cells to vasoconstriction stimuli, thus to increased vasoconstriction.

Increase in left ventricular systolic and diastolic load—the second vicious cycle in heart failure: This second vicious cycle originates in the first one. The increase in total peripheral resistance helps maintain arterial pressure but increases the afterload, causing the left ventricle to work harder. Venous constriction and sodium retention increase venous return and thoracic blood volume. This is a beneficial effect as long as the increase in cardiac filling pressure is accompanied by an increase in ventricular ejection fraction (Starling mechanism). Beyond a certain pressure, however, this mechanism is no longer effective. But regardless of the effectiveness of this adaptation mechanism, it causes an increase in intraventricular diastolic pressure, and thus an increase in diastolic work load.

Thus, these mechanisms that work to compensate for the failing heart can end up increasing the cardiac work load, which is the second vicious cycle.

TREATMENT OF CONGESTIVE HEART FAILURE

Mild CHF can be treated by breaking either of these 2 vicious cycles, the vasoconstriction/sodium retention/vasoconstriction cycle or the increase in LV systolic and diastolic pressures that increase the work load of the failing heart.

The effectiveness of diuretics in the treatment of CHF is so well known that they may sometimes be forgotten because newer forms of treatment, such as angiotensin-converting enzyme (ACE) inhibitors, e.g., appear more sophisticated. But this takes an overly simplified view of the mechanism of action of diuretics in CHF.

By reducing circulating blood volume, diuretics alleviate the symptoms of heart failure, especially the edema and the congestion. Diuretics, by inducing acute volume depletion, activate the renin-angiotensin-aldosterone system, and this enhanced effect of aldosterone on the distal tubule needs to be blocked. This can be achieved by combining loop diuretics (such as furosemide) and potassium-retaining agents (such as spironolactone). When administered concomitantly with a thiazide diuretic or furosemide, spironolactone has an additive natriuretic effect resulting in greater sodium and water excretion with the combination than when either is administered alone. In addition, and most important, spironolactone reverses the potassium/magnesium depletion frequently associated with diuretic therapy.

Diuretics historically were the first treatment for CHF, but over the last 15 to 20 years, nitrates, vasodilators, α-receptor blockers and ACE inhibitors, by different pathways, have all been shown to improve cardiac hemodynamics, alleviate the symptoms of heart failure, and especially improve exercise tolerance, at least in the short to medium term.

Vasodilators, although quite effective, have to be used cautiously because of their adverse effects, and although diuretics remain by and large the drug of choice for mild CHF, they are themselves not devoid of adverse effects. In addition to promoting sodium excretion, they promote potassium excretion, leading to hypokalemia in 50% of the cases.[3] Because diuretic-induced potassium depletion is often accompanied by hypomagnesemia, the treatment of hypokalemia is not always a simple matter of replacing potassium losses. In addition, low serum potassium levels do not necessarily reflect the true extent of the problem, which is reduced intracellular potassium and magnesium levels that are difficult to detect. These set the stage for arrhythmias that are especially hazardous given the already compromised cardiac function of the patient with CHF. Recent studies have shown that most patients with CHF die suddenly and that the most likely cause is ventricular tachyarrhythmia. The British Medical Research Council Trial demonstrated a clear-cut relation between the development of hypokalemia and ventricular extrasystoles in a subset of patients receiving long-term diuretic therapy.[4] In addition, significant correlations have been found between frequency of ventricular premature contractions and low levels of plasma potassium and magnesium.[4]

Thus, given the fact that potassium depletion may be refractory to repletion, rather than trying to correct a deficiency, it would be much easier to avoid the deficiency in the first place, by using potassium-sparing diuretics such as spironolactone. In some European countries, potassium supplements are used sparingly. In France, spironolactone, either alone or in combination with furosemide or a thiazide, is the most widely used diuretic.

My discussion on diuretics has emphasized their preeminent role in managing patients with silent heart failure and in managing patients with mild to moderate degrees of CHF. In patients with advanced CHF, a judicious trial of high doses of diuretics and low doses of ACE inhibitors can be undertaken.

The success of diuretics in the treatment of CHF validates those concepts developed earlier; neuroendocrine adaptation eventually becomes neuroendocrine disturbance, worsening the heart failure. We can act on the vasoconstrictor mechanisms and we can stimulate vasodilator systems, so that treatment of cardiac failure by decreasing the work load of the left ventricle is an absolute necessity.

One way of preventing the progression of silent to overt CHF is early intervention, which means early diagnosis. Recently, echocardiography and thallium-201 perfusion imaging have become widely used techniques for the detection and diagnosis of cardiovascular disorders. They have the advantage of being noninvasive and show very clearly any changes in LV structure and function. Thus, these techniques can assist in detecting heart failure long before it becomes clinically overt, allowing therapeutic intervention before damage to the heart becomes

widespread and perhaps irreversible. When heart failure is detected early, i.e., when still in its silent stage, a rational basis for diuretic intervention exists, with the potential for limiting progression to more severe stages of CHF.

Because it is clear that hypertension, especially in the long term, may well lead to LVH and hence to CHF, it can be legitimately viewed to some extent as an important precursor of heart failure. If not adequately controlled, it will almost certainly eventually result in heart failure. So, although routine echocardiography or radionuclide imaging of patients with hypertension of several years' duration, in the absence of clinical signs of heart failure, may seem expensive, it is still considerably less expensive than treating the decompensated heart later.

CONCLUSION

Diuretics are still the best prevention: Primarily, hypertension should be prevented from progressing to heart failure. Because many antihypertensive agents have direct and indirect effects on the heart's function and structure, diuretics are still the first line of therapy for hypertension. However, although they are extremely effective in hypertension, their effect on serum electrolytes means that they have the potential of leading to hypokalemia and hypomagnesemia. The use of a potassium- and magnesium-sparing diuretic, such as spironolactone, is a reliable and effective safeguard.

REFERENCES

1. Kannel WB, Castelli WP, McNamara PM, McKee PA, Feinleib M. Role of blood pressure in the development of congestive heart failure: The Framingham Study. *N Engl J Med 1972;287:781–787.*

2. Kannel WB, Sorlie P. Hypertension in Framingham. In: Paul O, ed. Epidemiology and Control of Hypertension. *Miami: Symposia Specialists, 1975;553–592.*

3. Parmley WW. Factors causing arrhythmias in chronic congestive heart failure. *Am Heart J 1987;114:1267–1279.*

4. Kopelman HA, Helfant RH. Treatment of hypertension and risk reduction: potential proarrhythmic effects related to diuretic therapy. *Practical Cardiology 1987;13:41–58.*